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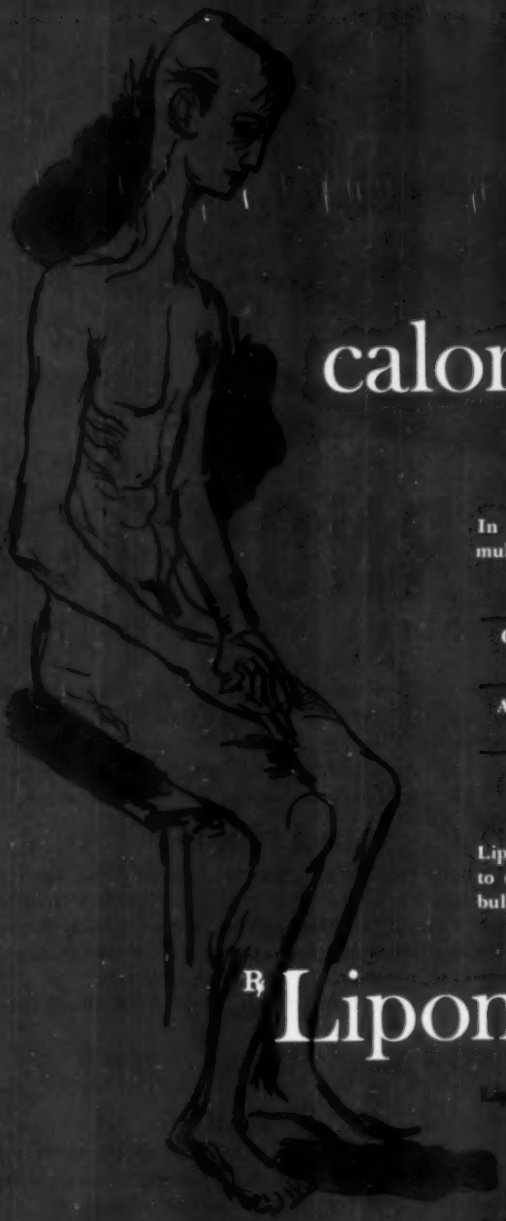

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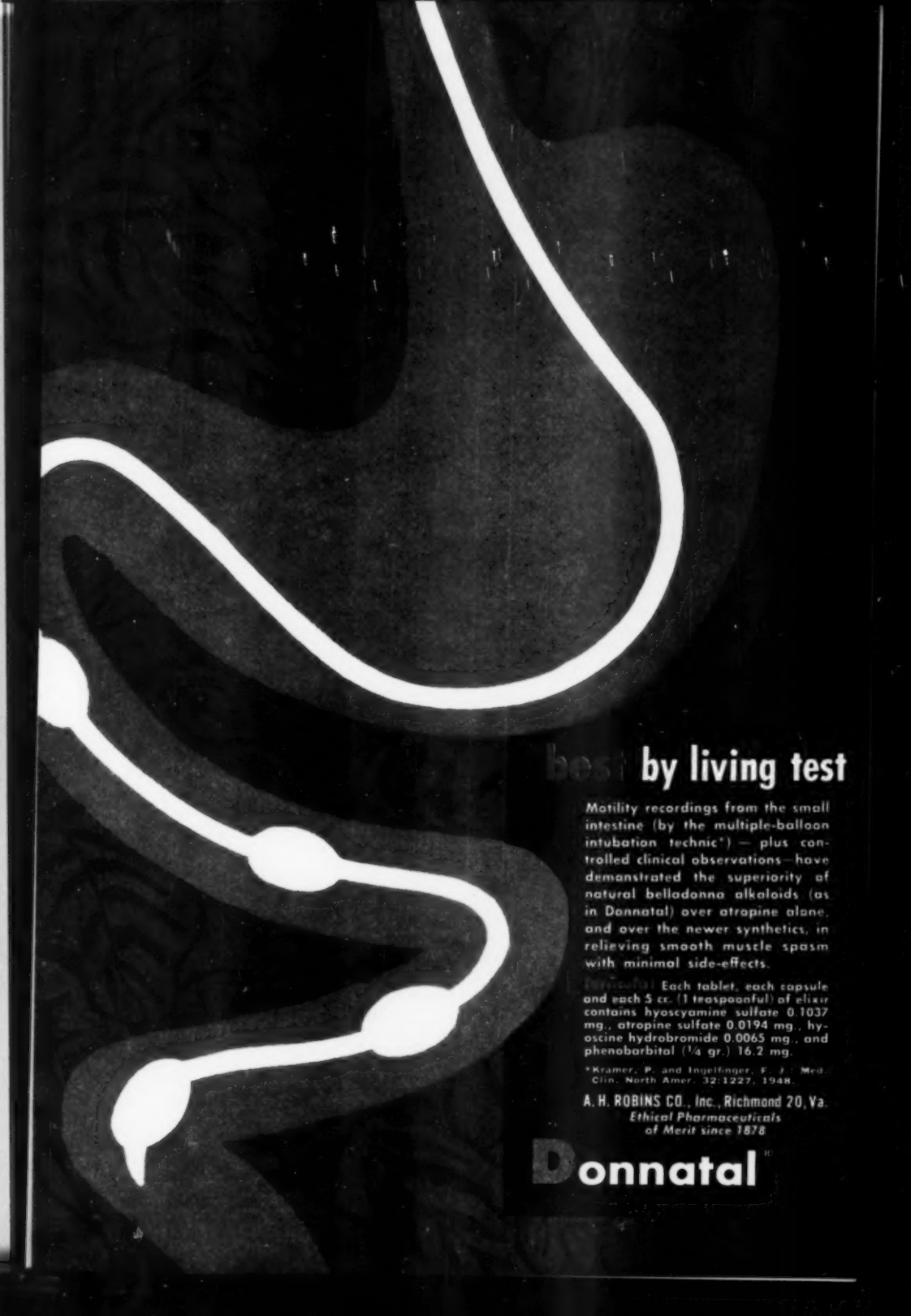

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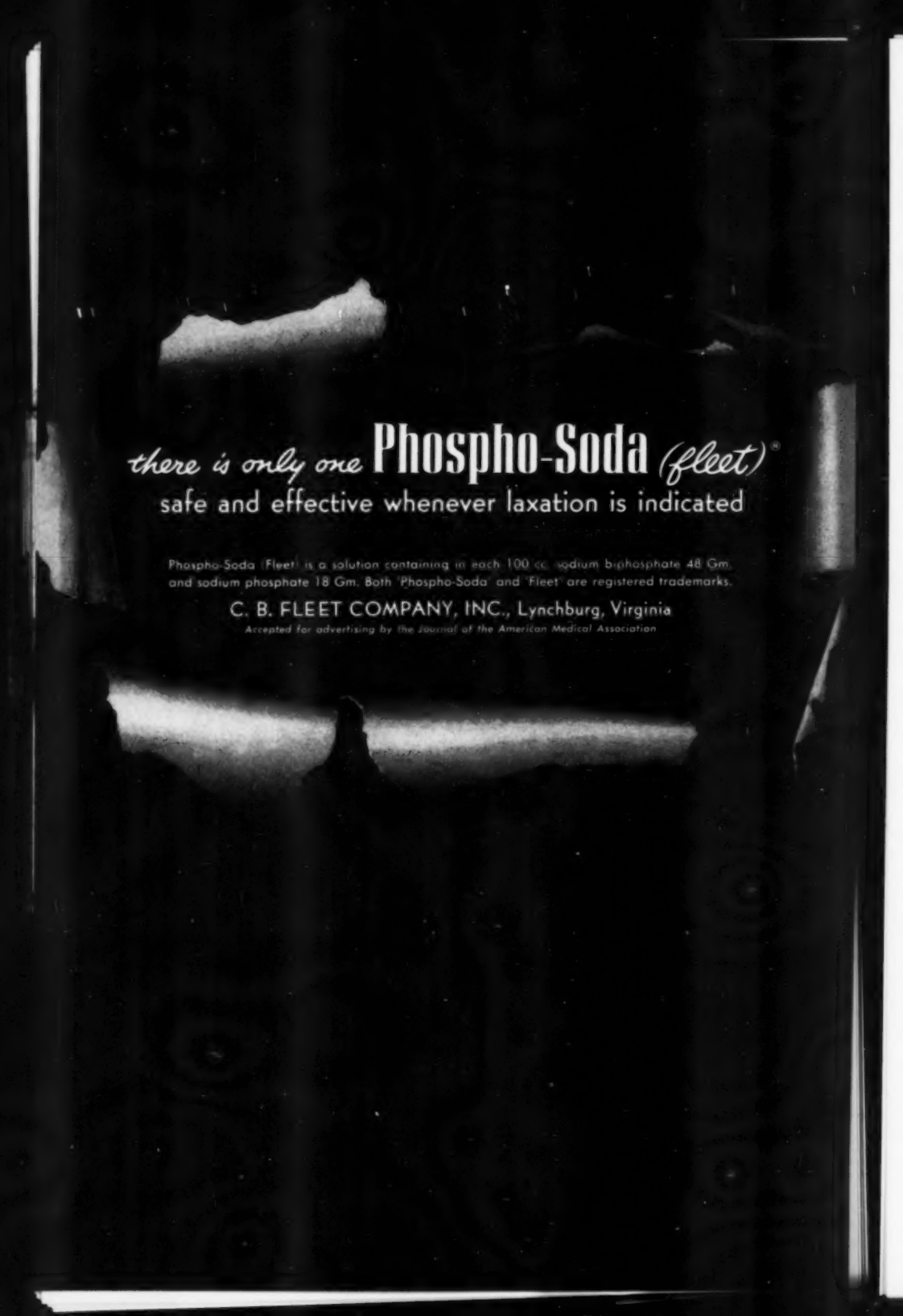
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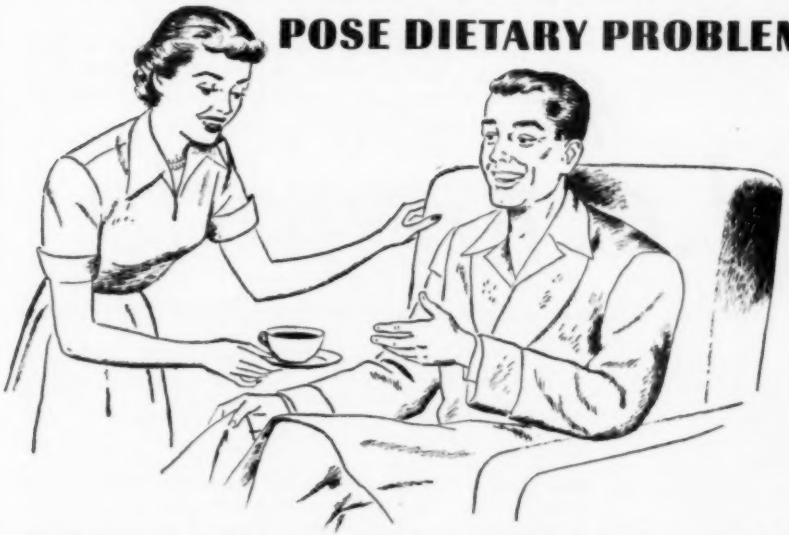

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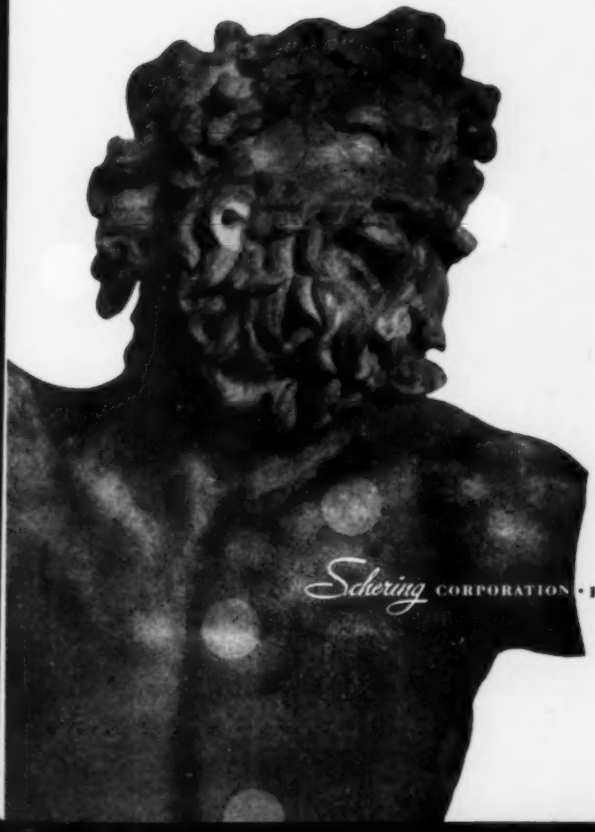

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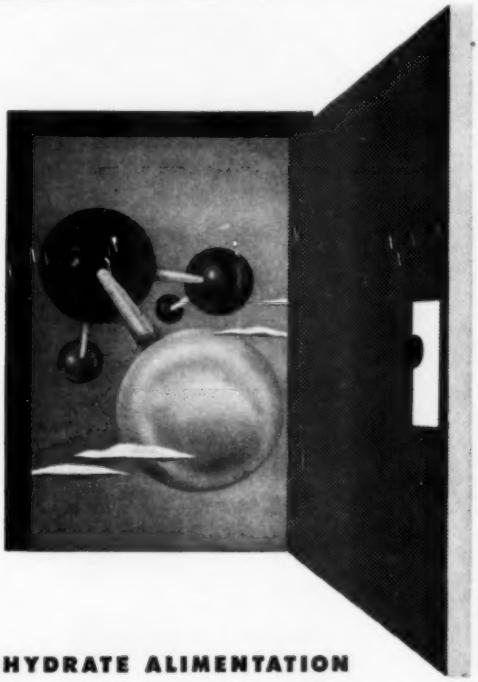

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ANNALS OF
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VOLUME 36 APRIL, 1952 NUMBER 4

THE MORPHOLOGY AND PATHOGENESIS OF CARDIAC FIBROSIS OF THE LIVER*

By ELI MOSCHCOWITZ, *New York, N. Y.*

INTRODUCTION

THE term "fibrosis" was purposely chosen instead of the conventional "cirrhosis" because the latter has too many connotations. Observers have displayed a wide diversity of opinion concerning the finer morphology and pathogenesis of the hepatic lesions associated with cardiac disease. There are a number of reasons for this: first, because the lesions were studied from a static rather than a biologic viewpoint; second, because the topography of the lesions was not controlled by serial section; third, because the genesis of the fibrosis was divorced from the vasculature of the liver; and fourth, because the significance of certain phases of the dynamics of cardiac failure was not sufficiently grasped.

This study was suggested by my observations on the pathogenesis of "congestive splenomegaly," [1] in which I tried to show that the lesions were explainable by a persistent hypertension of the portal circulation sequential to cirrhosis of the liver, chronic obstruction of the portal and splenic veins, chronic thrombosis and endophlebitis of the hepatic veins and, finally, to certain types of cardiac disorders. In these cardiac disorders the severest lesions in the spleen were observed in constrictive pericardium, in which a peripheral venous pressure is usually maintained, often over a span of years. The liver in such cases revealed an unusually severe fibrosis, the so-called "pseudocirrhosis," a term first suggested by Pick,[2] and it is in the attempt to interpret the pathogenesis of this fibrosis that this study was initiated. For this purpose, the livers of six cases of constrictive pericardium were studied, one of which was associated with a mitral stenosis, and a second with tricuspid stenosis; four cases of tricuspid stenosis, a disorder in which

* Received for publication August 10, 1951.
From the Laboratories, Department of Pathology, The Mount Sinai Hospital, New York, N. Y.

the circulatory dynamics are analogous to those in constrictive pericardium; six cases of tricuspid insufficiency (all associated with mitral stenosis), in which the history of prolonged failure and the presence of a "congestive splenomegaly" left no doubt that portal hypertension was maintained over a long period; and, finally, four cases of thrombosis of the hepatic veins, two fresh and two organized. The organized thromboses were associated with a fairly advanced "congestive splenomegaly." Four of the livers in constrictive pericardium were available for study by serial sections, one of tricuspid stenosis, and three of tricuspid insufficiency. The sections were stained with hematoxylin eosin; some by van Gieson's stain, the azan modification of the Mallory stain for reticulum, and the Weigert stain for elastic fibers. In addition, many hundreds of slides of livers from cases of various types of cardiac failure were examined.

In the hepatic fibroses, different stages of the process were studied, so that a fairly consistent gradation from the earliest to the latest phases was elicited. Broadly, the livers could be divided into two groups: first, those in which prolonged portal hypertension was absent, and second, those in which it was present. The distinguishing feature between the two was the presence of "congestive splenomegaly."

1. *The Morphology of the Liver in Cardiac Disease Without Prolonged Portal Hypertension:* These are the lesions familiarly described in the "nutmeg" liver. In the earlier phases, there is dilatation of the central vein and of the radiating sinusoids for varying distances into the lobule, with consequent narrowing of the hepatic cords. Somewhat later, fatty and parenchymatous degeneration of the hepatic cells in these areas ensues. During the progress of cardiac failure, extensive centrolobular necrosis may occur, with more or less complete disappearance of the capillaries. In extreme cases, necrotic areas coalesce between the lobules, leaving a zone of varying width of intact liver cords surrounding the portal spaces. Within these necrotic areas the remains of the reticulum around the capillaries are always visible, but the reticulum is condensed and not increased in quantity. The portal spaces and the interlobular septa show no changes. The hepatic veins are dilated. For obscure reasons these changes are not uniform throughout the liver but vary in intensity in different areas. They are more pronounced in the subcapsular zone, we believe because of the resistance offered by the capsule. During these phases the individuals have passed through episodes of failure, but the rise in peripheral venous pressure and the concomitant portal pressure are comparatively transient and not sufficiently prolonged to produce further damage.

2. *The Morphology of Hepatic Fibrosis in Cases with Prolonged Portal Hypertension:* A prolonged portal hypertension is evidenced by the omnipresent "congestive" or, better termed, portal hypertensive splenomegaly. In every case in which the peripheral venous pressure was recorded, it was elevated, varying between 16.5 and 29.5 mm. of mercury. The lesions in

the spleen are identical but are not so severe as those observed in hepatic cirrhosis or chronic obstructions of the portal or splenic veins; first, as I pointed out,[1] because the obstruction is central and is therefore not so consistently high as in the more peripheral obstructions; and second, and this is the main reason, because the span of life in cardiac disorders is small as compared to chronic obstructions of the portal tract. In other words, it is the duration and not the degree of portal hypertension that is crucial. The lesions in these livers are severe and affect every histologic component of the liver.

A. *The Sinusoids and Central Veins:* In the earlier phases the sinusoids, especially around the central veins, are more widely dilated and form at times veritable "blood lakes." The liver cords are severely compressed and the connective tissue walls of the sinusoids are much thicker than normal (figure 1.) This phase I have interpreted as a capillary sclerosis, and in every instance where it was at all marked it was associated with sclerosis of the hepatic veins.[3, 4]

The capillaries are affected in other ways. In the normal hepatic lobule the capillaries converge uniformly from the periphery to the central vein. In these fibrotic livers, short circuits are observed, as manifested by a slightly curved arrangement of the liver cords within the lobule and in serial sections; these represent the capillaries that normally arise only from the tips of the portal veins that pass in the interlobular septa, and thence flow as in a shunt directly into the central vein. Figure 2 is a fortunate section that reveals this in one plane. With the higher power, these shunted capillaries are usually narrower than the remainder, the surrounding trabecular cells are paler and the intervening sinusoids show a capillary sclerosis. These shunts within the lobule represent the earlier phases of more pronounced communications between the portal spaces and hepatic veins, later to be described.

While centrolobular necrosis is occasionally observed in such livers, these necrotic areas usually reveal various stages of organization and fibrosis. Many observers have maintained [5-9] that the fibrosis occurring in these areas is the result of a condensation of the reticulum. On the other hand, Herxheimer [10] showed that there is a definite increase in the quantity of reticulum (Gitterfasern). I have been able to follow the progression from necrosis to fibrosis in a number of instances, and it is plain that the genesis of the fibrotic process is identical in the liver to that occurring in necrotic areas in any other organ, namely, by the formation of granulation tissue. At first the products of the degenerative trabecular cells are absorbed. Many of the cells become shadow cells, and there are blood pigment and abundant nuclear fragments (figure 3). This is followed by the invasion of cells, mostly lymphocytes, with occasional plasma cells and polymorphonuclears (figure 4). Subsequently the lymphocytes undergo fibroblastic transformation, and eventually capillarization of these foci results, either by autochthonous formation, as in the embryonal mesenchyme,[11] or by the sprouting of capillaries

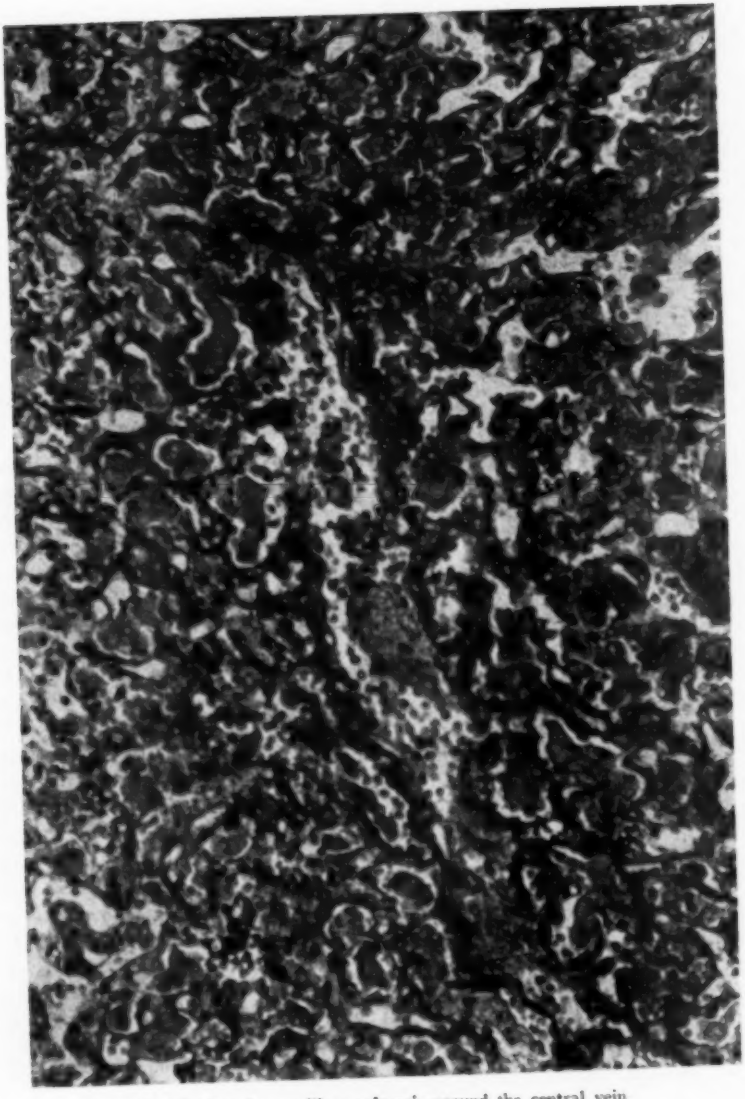

FIG. 1. Showing capillary sclerosis around the central vein.

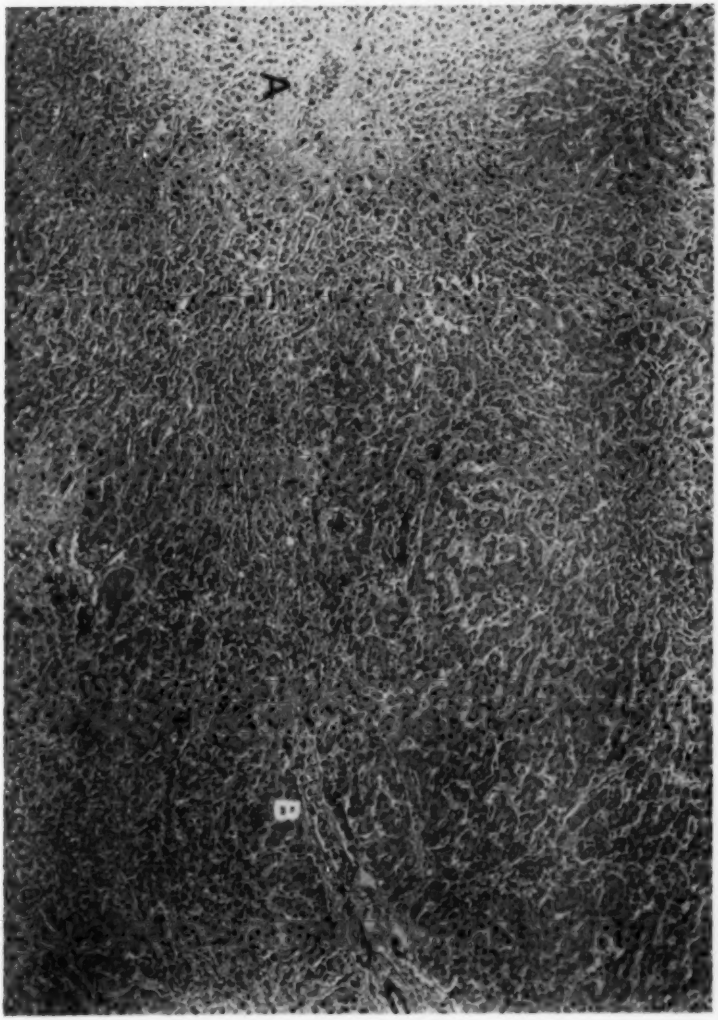

FIG. 2. Showing a direct shunt within the lobule between the terminal capillaries of the portal vein in an interlobular septum and a central vein. (a) Central vein. (b) Interlobular septum. Case of mitral stenosis and tricuspid insufficiency.

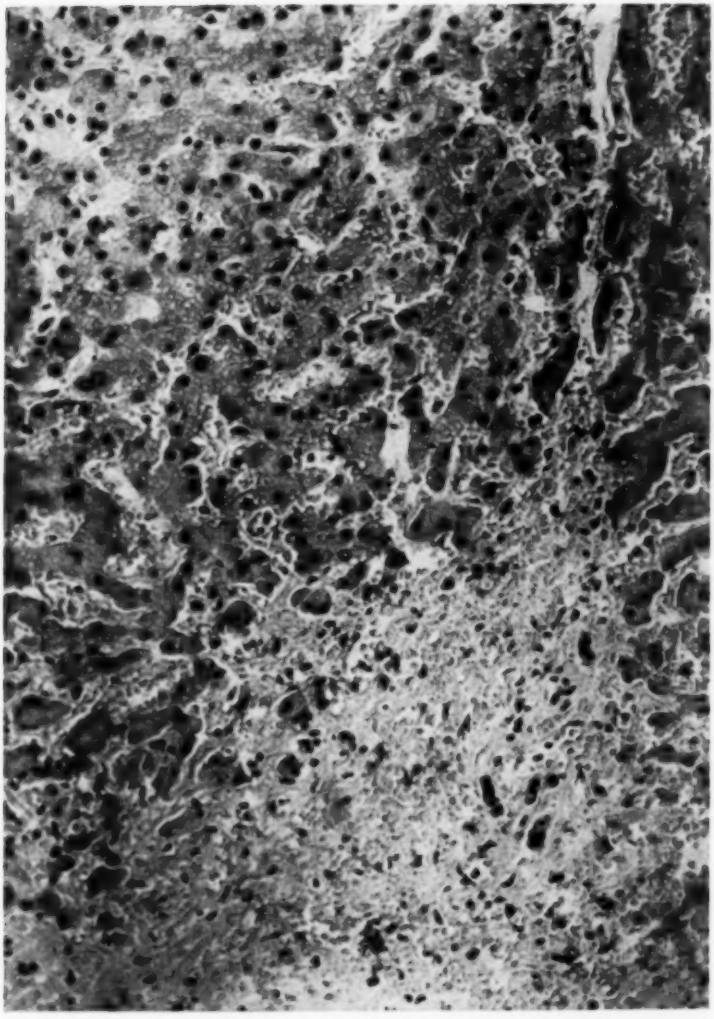

FIG. 3. Area of centrolobular necrosis. Case of tricuspid stenosis and mitral stenosis.

or venules from the terminal ends of the portal veins in the interlobular septa (figure 5). These capillaries either remain as such or develop into small venules which possess a delicate muscular wall. In serial sections they communicate with the sublobular or hepatic veins on the one hand, and with the

branch of portal veins within the interlobular septa on the other. In other words, these capillaries and venules represent newly formed central veins. In the final stage these foci are composed of collagen, usually dense in the central areas, in which there is occasionally hyaline degeneration, and the

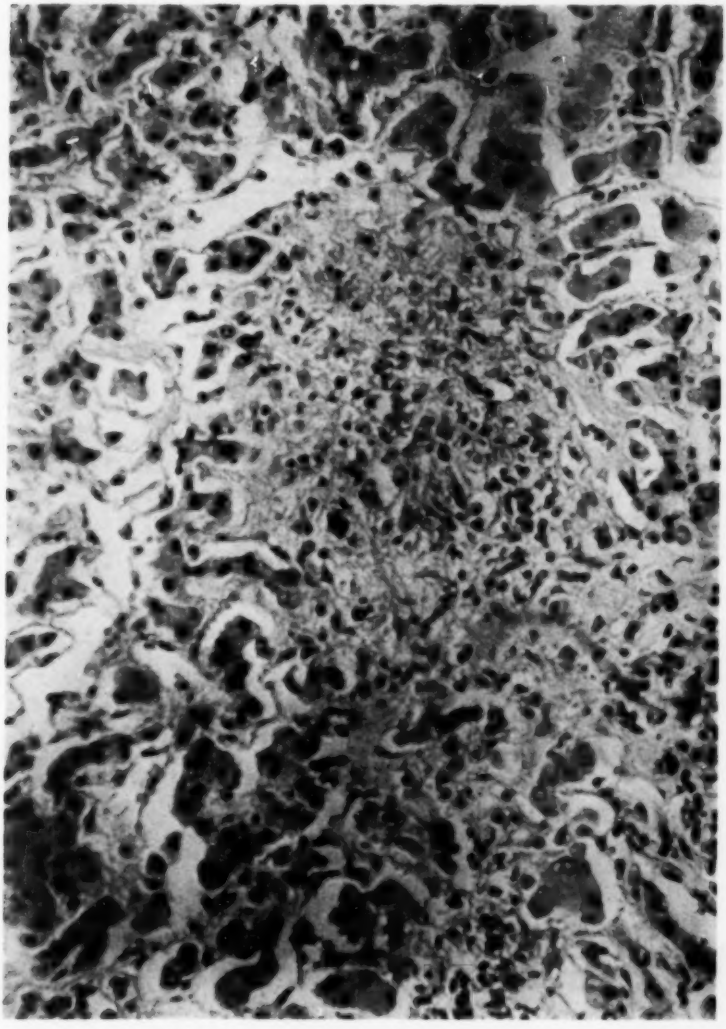

FIG. 4. Area of centrolobular necrosis showing beginning organization. Case of tricuspid insufficiency and mitral stenosis.

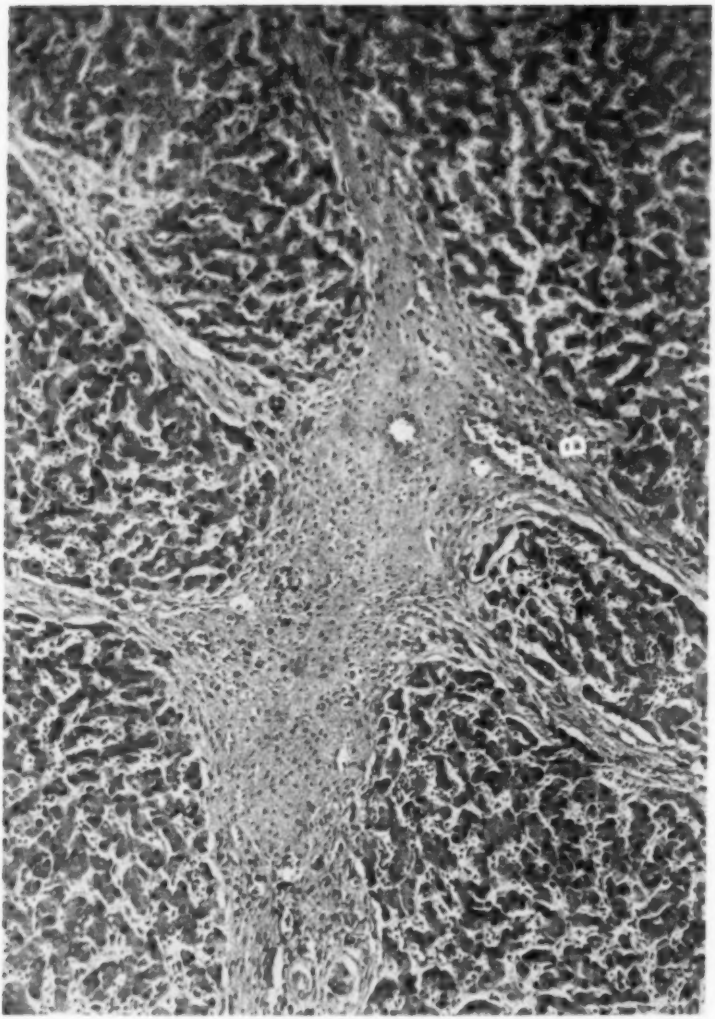

FIG. 5. A fully healed area of centrolobular necrosis, showing a sprout of portal vein from an interlobular septum (b). It also shows the characteristic scalloped shape due to the communications with the adjacent interlobular septa from the portal septa, and numerous capillaries and venules within the foci. These represent the newly formed central veins. In such livers, central veins are absent in their normal sites.

foci are interspersed with many fibroblasts, often remains of liver cords that have escaped destruction, newly formed bile canaliculi, especially along the margins, and a variable number of capillaries and venules (figure 5). Topographically these foci conform to the areas of necrosis, that is, they are either exclusively centrolobular or are joined with the foci in the neighboring lobule or lobules. They thus appear patchy, and have been so described,[5-7] or as more or less broad wavy bands that, by serial section, course extensively throughout the hepatic parenchyma. Inasmuch as in the terminal stage the interlobular vascular septa from the adjacent portal spaces invariably communicate with these foci, they appear scalloped or star-shaped (figure 5). The margins are usually sharply defined, as in the primary necrotic foci, or there may be a narrow zone of capillary sclerosis. It is curious to note that in the most advanced stages the central veins are completely absent in their normal sites. They have been replaced within these organized foci by the newly formed capillaries and by the sprouting venules from the adjacent portal spaces.

Most students of "cardiac cirrhosis" assume that the fibrosis is a replacement fibrosis. We believe that it is an active and proliferative process and represents a medium for the development of new capillaries and venules.

B. *The Hepatic Veins:* The walls of these veins are widely dilated and are invariably thickened, usually to an extreme degree (figure 6). The intima is also thickened and often appears loose and edematous. The phlebosclerosis involves the entire venous tract of the organ, including that portion that enters directly into the vena cava.[8] The thickening involves not only the walls of the vessel but also the immediately surrounding parenchyma, which shows a narrow zone of capillary sclerosis often interspersed with newly formed bile canaliculi. This I believe to be the result of pressure. Often one sees a straight, thick, almost acellular band of fibrous tissue coursing through the parenchyma, apparently without any connections, or attached at one end to a hepatic vein. On serial section these represent merely the wall of a hepatic vein. A considerable portion of the fibrosis in such livers is therefore the result of the phlebosclerosis of the hepatic veins, and in advanced cases the liver may be viewed as a labyrinth of tunnels with only a comparatively small amount of glandular parenchyma between. Rarely one notes organization of a thrombus within a hepatic vein.

C. *The Portal Spaces:* The larger portal spaces are usually intact. Some contain a smaller or larger deposit of lymphocytes, but these are common in many livers in the adult years and are of little significance. I have not observed fibroblastic transformation of these deposits as in true Laennec's cirrhosis. The smaller portal spaces, that is, those that Mall [12] designated as of the fourth to sixth order, are usually intact, but the containing venules are more conspicuous because they are dilated. A few of these smaller portal spaces are deformed or lost within the extensive areas of fibrosis. Occasionally one notes along a margin of a portal space what appears to be

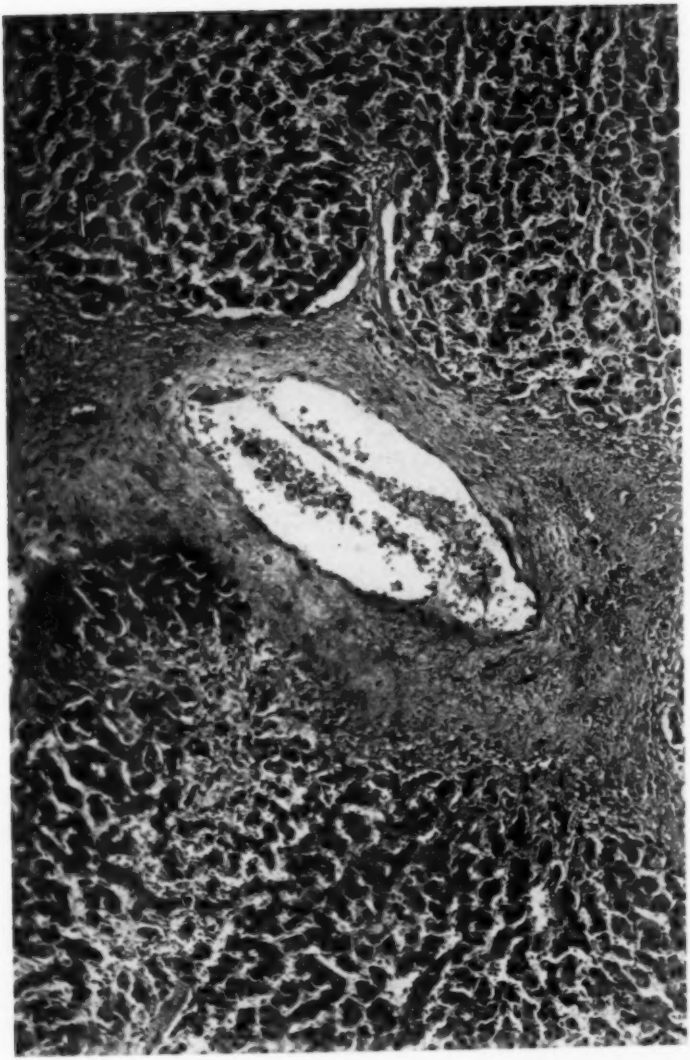

FIG. 6. Showing phlebosclerosis of a hepatic vein. Case of constrictive pericardium.

an area of periportal fibrosis; on serial section, however, these are shown to be either the normal but excessively vascularized connections between adjacent portal spaces, or an impingement of the organized centrolobular necrotic area upon the margin of the portal space, or only the circumferential wall of a smaller or larger interlobular vascular septum as it penetrates into the lobule.

The periportal fibrosis that has been so frequently reported in "cardiac cirrhosis" is therefore specious, and it is not synonymous with true Laennec's cirrhosis. The hypothesis that the congested liver renders the organ susceptible to Laennec's fibrosis is untenable. In this we agree with Piery,[13] Eisenmenger,[14] Herxheimer [10] and Lambert and Allison.[8]

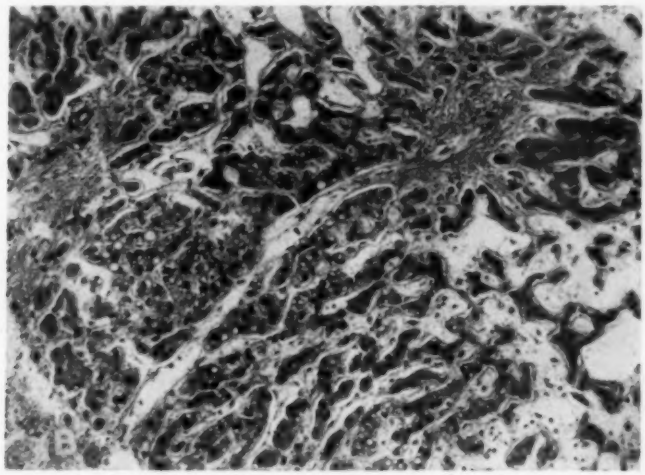

FIG. 7. Showing newly formed capillary sprouts from portal venule (b) and entering sclerotic central vein. Case of tricuspid insufficiency and mitral stenosis.

That cardiac fibrosis may be associated with a true Laennec's cirrhosis was revealed in the case of a 14 year old boy who had a constrictive pericardium but who died from nonspecific ulcerative colitis. The liver showed some of the early features of a cardiac fibrosis, but there was a conspicuous Laennec's cirrhosis, as evidenced by fibroblastic transformation of the portal spaces with capillarization, the formation of pseudolobuli, the displacement of the central veins and the sprouting of new venules and bile ducts into the parenchyma, all ear marks of a true Laennec's cirrhosis.[21] There is no reason to doubt that the cirrhosis was caused by the undernutrition attendant upon his ulcerative colitis and not to his cardiac disorder. The association of Laennec's cirrhosis and ulcerative colitis is not uncommon.

When arterial hypertension is part of the cardiac disorder, the hepatic arteries within the portal spaces show hyperplastic arteriosclerosis.

D. *The Vascular Septa:* The changes arising in these structures from sustained portal hypertension of cardiac origin are remarkable, and they contribute largely to the finer morphology of cardiac fibrosis. In the normal adult liver, the number of septa arising from each portal space is comparatively small, and depends upon the order in point of size of the portal space. The septa contain, aside from the connective tissue, a branch of the portal vein, a somewhat smaller hepatic artery and a bile duct. Under normal conditions, the septa are comparatively narrow and short. In the cardiac fibroses, the septa are wide and usually extend for long distances into the parenchyma. In addition, new vascular septa arise from a small surface branch of the portal vein within the portal spaces. These are of capillary dimensions and communicate with the centrolobular organized foci described previously. Figure 7 shows nicely such a capillary entering a central vein surrounded by a zone of capillary sclerosis. In other areas, these intercommunications are represented by short narrow bands of fibroblastic tissue. These were once vascular channels, as proved by the presence in many of narrow capillaries. In other words, here again another extensive series of short circuits from newly formed capillary vessels arises between the portal veins and the newly formed central veins.

Not only the new but also the preëxisting interlobular septa communicate with the organized centrolobular areas. At first blush the septa appear to be composed of cellular fibrillar connective tissue only, but on serial sections these contain terminal capillary branches of the portal vessel (figure 9). Their communication is usually fanwise, and is accompanied by the small bile duct of the interlobular septum. Not all of the vascular septa behave in this manner, only those that arise from the fourth to sixth order of portal spaces. In the unaffected areas the interlobular septal portal branch breaks up normally into fan-shaped branches of capillaries (figure 9) which merge imperceptibly with the lobular sinusoids, but in affected areas these capillaries proliferate and become sclerotic (figure 10). Apparently the stimulus also causes an extensive proliferation of bile canaliculi in the terminal portions of the interlobular septa.

There is another extraordinary series of shunts in these cardiac fibroses, namely, direct communication between the portal veins in the interlobular septa and the hepatic veins. Sometimes the portal vein in the interlobular septum opens by way of capillaries directly into the hepatic vein. Figure 11 is a section that shows this in one plane. Others show it only serially. More often the communication is by fan-shaped sclerosed capillaries that enter either directly into the hepatic vein (figure 12) or into the vasa vasorum of the vein (figure 13).

In summary, four kinds of shunts or short circuits between the portal and hepatic veins may be observed: (1) between the interlobular portal vein

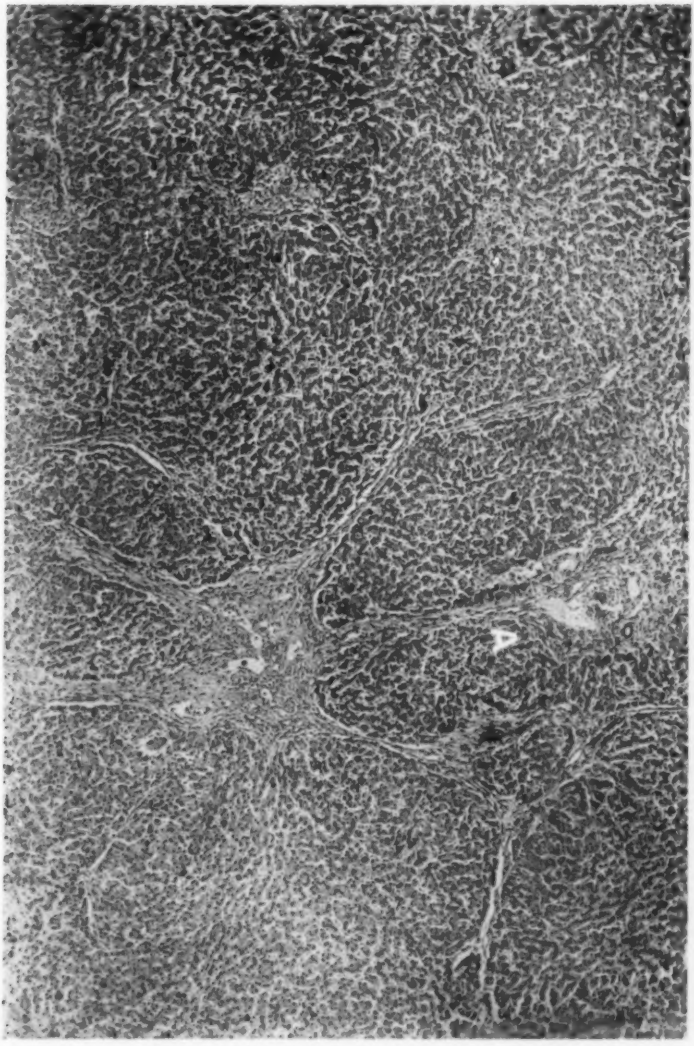

FIG. 8. Showing organized area of centrolobular necrosis, with numerous vascular communications with portal spaces, one of which (a) can be distinctly seen. The others can be demonstrated in serial sections. Case of constrictive pericardium. Note absence of central veins in their usual sites.

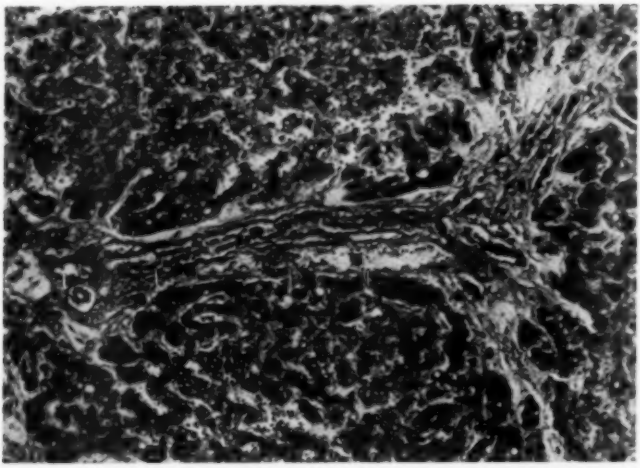

FIG. 9. Showing portal vein from interlobular septum breaking normally into terminal capillaries. Case of tricuspid insufficiency and mitral stenosis.

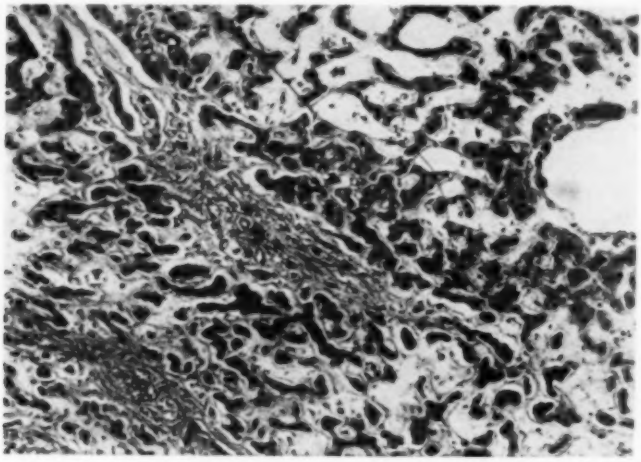

FIG. 10. Showing terminal end of an interlobular septum breaking into sclerotic capillaries. Case of tricuspid insufficiency and mitral stenosis.

and the central vein (this morphologically is an early phase); (2) between newly formed capillaries arising from the portal veins in the portal spaces and the newly developed central veins in the centrolobular organized fibroses; (3) between the preëxisting portal veins in the interlobular septa and the

central veins in the centrolobular organized fibrosis; and (4) direct communications by a capillary network between the portal veins in the interlobular septa and the hepatic veins. The last three represent later phases. In other words, the liver has been converted into a modified Eck's fistula, the communications between the portal and the hepatic veins being entirely capillary in nature. There is no doubt that these shunts diminish hepatic function, an observation that has been amply demonstrated in Eck's fistulae. Nevertheless they represent a compensatory attempt at restoration of function.

The fibrosis in the advanced phases of cardiac disease when portal hypertension is maintained for a sufficiently long period is therefore compounded of a number of lesions: (1) capillary sclerosis, which occurs in a number of sites: (a) around the central veins; (b) at the terminations of portal veins in the interlobular septa, and (c) in various shunts between the portal vein terminals and the central or hepatic veins; (2) the organization of centrolobular necroses; (3) phlebosclerosis of the hepatic veins and the adjacent zone. These topographic distributions of the fibrosis help clarify the descriptions current in most reports, where such vague terms as "patchy," "diffuse," "intralobular" and "interlobular," and "peripheral" are employed. It is essential to recognize these structural relations in order to interpret the pathogenesis.

E. *The Capsule of Glisson:* In all six cases of constrictive pericardium the capsule was thickened (zuckerguss). It was surprising to find that, of the eight cases of tricuspid lesions, three (or 37.5 per cent) showed a thickening of the capsule. This is too large a percentage to be ascribed to mere chance. It is noteworthy that in these instances the fibrosis was more intense and widespread, so that it could be surmised that increased tension in the venous channels within the organ may be the cause of the thickening of the capsule. Some confirmation of this presumption is furnished by the morphology of congestive splenomegaly. In 10 of 18 cases of Laennec's cirrhosis the splenic capsule was thickened, and as a rule the larger the spleen the greater the thickening.[1]

The hepatic fibrosis resulting from cardiac disease was not evenly distributed throughout the organ, aside from its prominence beneath the capsule. Often two sections taken from different parts of the liver would show wide variations in intensity; this was occasionally manifest in the same section. Inasmuch as most of the studied material was old, it was impossible to trace the sites from which the sections were removed. But apparently there are variations in the blood supply of the liver that are not completely understood. In this connection the observations of Wakim and Mann [22] are suggestive. They show that, in animals studied with the technic of quartz rod illumination, under normal circumstances the activity within the sinusoids varies in different areas of the same field: while some are closed, others are widely open.

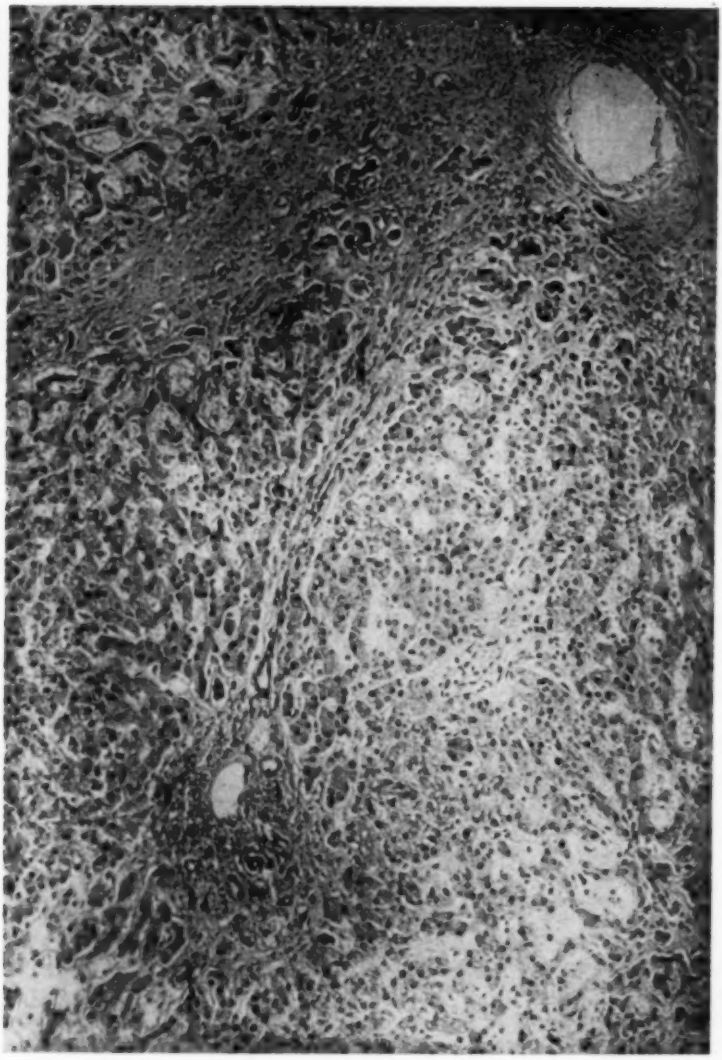

FIG. 11. Showing fan-shaped group of sclerosed capillaries spring from the portal vein in an interlobular septum and communicating with a hepatic vein. Case of tricuspid insufficiency and mitral stenosis.

FIG. 12. Showing portal vein in an interlobular septum communicating by direct capillaries with a hepatic vein (c).

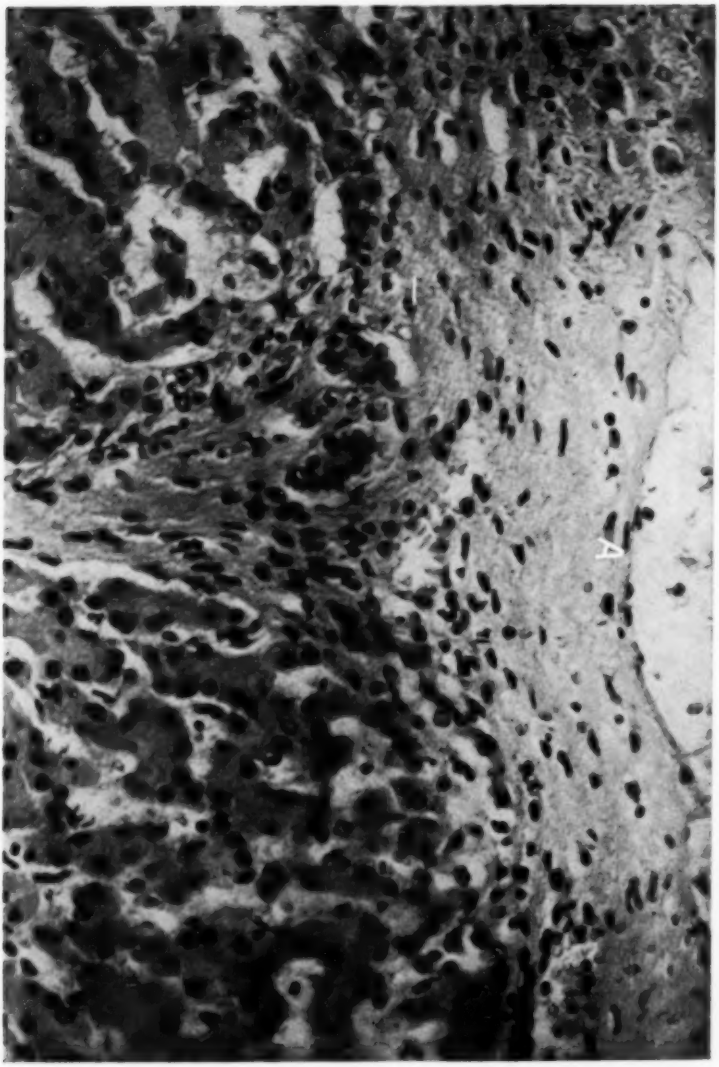

FIG. 13. Showing fan-shaped group of sclerosed capillaries springing from the portal vein in an interlobular septum and communicating with vasa vasorum of a hepatic vein. Case of constrictive pericardium.

We noted no evidence that the hepatic artery in the portal septa took part in the above process.

Although the morphologic change is more severe in constrictive pericardium, an observation that accords with others,[6] identical changes, although less severe, were noted in the cases of tricuspid disease. They were less severe in the cases of tricuspid insufficiency than in tricuspid stenosis. No attempt was made to discover whether hepatic fibrosis occurred in other cardiac disorders. The probability is strong that it does under the auspices that we have predicted. Interest was centered not on a statistical study but mainly upon the morphology and pathogenesis of the lesions.

Pathogenesis: Practically all students [5-10, 13] of "cardiac cirrhosis" refer to "congestion" and "stasis" as the main causes of the fibrosis, and state that such livers are usually found in individuals who have had repeated attacks of cardiac failure. These observers have fallen into the common error of assuming that "congestion" and "stasis" are synonymous with increased venous pressure. The difference is obvious in the clinical study of cardiac failure. The venous pressure only becomes elevated during periods of failure. When compensation is restored the venous pressure returns to normal, although clinical and even anatomic evidences of congestion remain. Congestion may be the result of factors independent of venous pressure. In uncomplicated cases of polycythemia vera, the systemic congestion is the result of an increase in the blood volume. In hyperthyroidism it is the result of an increased blood flow.

That portal hypertension of central origin * was the cause of the fibrosis was brought to focus in the study of the livers in six cases of constrictive pericardium, in which, we repeat, an increased peripheral venous pressure is maintained.

Under normal conditions the pressure in the portal vein in man, according to Bellis,[15] is between 14 and 22 mm. of normal saline solution. This pressure is sufficient to propel the portal blood to the hepatic vein at its entrance to the vena cava, where the pressure is around zero. The pressure within the hepatic veins in constrictive pericardium has not to my knowledge been measured, but it must be considerably higher than normal, because in every instance that we have studied the hepatic veins at their entrance into the vena cava show a profound sclerosis. This increased pressure implies that the flow of blood from the portal vein meets with an increased resistance. As a consequence, the central vein of the lobule and its tributary capillaries dilate, the liver cords become compressed and, if the pressure is maintained, capillary sclerosis in these areas ensues. In this respect the liver behaves like other parenchymatous organs when the main efferent or afferent vessels are subjected to an increased pressure, and therefore the vessels acquire hyperplastic arteriosclerosis or phlebosclerosis, as the case may be. We

* Obviously portal hypertension resulting from chronic obstruction of the portal and splenic veins cannot produce hepatic fibrosis, since the obstruction is distal to this organ.

refer to the capillary sclerosis that occurs in the alveolar capillaries in hypertension of the pulmonary circulation; to the capillary sclerosis of glomerular capillaries in systemic hypertension; to the sclerosis of the capillaries within the splenic cords in "congestive splenomegaly," and to the capillary sclerosis of the islands of Langerhans in systemic hypertension.[4]

There is every reason to believe that anoxia associated with right-sided cardiac failure, especially if accompanied by shock of 24 hours' duration, is the cause of the centrolobular necrosis.[23] It seems curious that the liver is the only organ that undergoes necrosis under circulatory failure in the absence of emboli, thrombosis or infection. Indeed, Mallory [16] invoked an infective or toxic factor, but there is a noteworthy absence of infection in our cases. Moreover, identical necroses have been produced experimentally by the simple mechanical method of obstructing the vena cava.[17] We suggest the following explanation. The liver is the only organ in the body which is predominantly supplied by venous blood. According to Burton-Opitz [18] and MacLeod and Pearce,[19] the hepatic artery supplies only a little less than one-third of the total blood supply of the liver. Moreover, the branches of the hepatic artery in the interlobular septa whose capillaries communicate with the sinusoids average only 8 microns in diameter, compared to a diameter of 9 or 10 microns for the branch of the portal vein. Inasmuch as the portal blood is more anoxic than that of the hepatic artery, the blood is further reduced in oxygen by the time it reaches the central vein, and so one anoxic factor is superimposed upon another.

An explanation is now in order for the development of new capillary vascular septa arising from the portal spaces, the increased capillarization from the terminal branches of the interlobular portal septa, and the remarkable shunts between the portal veins and the central and hepatic veins under the influence of portal hypertension. These are explainable by the laws of Thoma.[20] These are: "(1) The width of a vessel is dependent upon the rate of the blood flow. When the rate lessens the width diminishes. (2) The thickness of the wall depends on the blood pressure. (3) The new formation of capillaries depends on the difference of pressure between the interior of the capillary and the surrounding tissue spaces. If in a certain area the pressure of the fluid is higher than the intracapillary pressure, the formation of capillaries does not occur. If, on the other hand, the intracapillary pressure is higher, new capillaries are engendered." These laws have withstood rigid tests and are generally accepted by morphologists.

The third law serves adequately to explain the formation of new capillaries under the influence of the portal hypertension and, according to Mall,[12] in his classic studies on the development of the liver, this is precisely what happens in the embryo. He says: "In the area vasculosa of the chick there is an extended capillary network in which no arteries or venous channels can be differentiated. A few channels however are selected by the blood stream in consequence of the general direction, which is given to it by the position of the end of the primitive aorta on the one side and the venous ostia

of the heart on the other. The channels contain the more rapidly flowing blood streams; they therefore dilate and become converted into arteries and veins. . . . The conversion of capillaries into arteries diminishes the resistance of the blood stream and leads to an increase in pressure in the capillaries. Then according to the third law of Thoma, new capillaries are formed at all places in the capillary area in which the pressure of the blood exceeds a certain limit. These capillaries again reduce the pressure by forming new connections between the arteries and the veins. *The third law therefore implies that during the growth of the organ, new capillaries are being formed everywhere and that after complete growth, the blood pressure* in all capillary areas of the same organ is fairly uniform." (Italics mine.)

The one difference between Mall's description of the formation of capillaries in the embryo and that observed in hepatic fibrosis of cardiac origin is that, instead of an artery, the portal vein, which in the liver is an afferent vessel, is subject to increased pressure. I have described [21] in Laennec's cirrhosis the sprouting of new capillaries from the smaller portal spaces that penetrate through the lobule and enter the hepatic veins. The formation of new sinuses in the spleen in "congestive splenomegaly" is a further example of the same mechanism. There is no doubt that the development of these new blood capillaries and the capillary shunts represents a compensatory mechanism to help equalize the pressure between the portal veins and the hepatic veins. If such a compensation were not possible the portal blood would not flow into the hepatic veins at all. Obviously it is unfeasible to measure the portal pressure in cardiac subjects, but the probability is strong that the pressure will be of the order of that of the median cephalic vein in the arm. Under any circumstances, even in the most advanced states of cardiac fibrosis, the pressure in the portal vein must necessarily be higher than in the hepatic vein at its termination.

How long portal hypertension in cardiac disease must be maintained before fibrosis begins it is at present impossible to determine. This might be gauged at some future time when a case of constrictive pericardium is observed throughout its entire cycle. The duration may also be determined by animal experiment. The only attempt to reproduce cardiac fibrosis experimentally was done by Zimmerman and Hillsman [17] in dogs by compression of the vena cava. They produced an active proliferation of fibrous tissue which remained purely central even after 85 days of observation. Whether this period was not sufficiently long, or whether the peripheral venous pressure was not elevated in these animals cannot be determined.

In our two cases of chronic obstruction of some of the hepatic veins, the fibrosis was entirely centrolobular and was limited to the areas of the liver which were obstructed. Nor would one expect to find a further progression, because on mechanistic grounds the venous pressure proximal to the entrance of the hepatic veins into the vena cava could not have been elevated.

Clinical Aspects of Cardiac Cirrhosis: These are of only academic interest,

because there are more vital issues involved. Nevertheless, the presence of an advanced fibrosis may be suspected given the proper auspices:

(1) If there is a constrictive pericardium of fairly long duration.

(2) If there is a persistent and recurring ascites. In only one of our cases was ascites absent. In this case, the calcification of the pericardium was incomplete. The ascites no doubt may be ascribed to an increased permeability of the capillaries in the portal area.

(3) If there is a prolonged maintenance of increased peripheral venous pressure in any cardiac disorder.

(4) If the spleen is enlarged. An enlarged spleen in a cardiac patient usually implies the presence of "congestive splenomegaly." This was absent in only one case of our series, a case of tricuspid stenosis.

(5) If there is a pronounced enlargement of the right auricle and ventricle and dilatation of the pulmonary artery. These latter evidences were absent in only one case of constrictive pericardium. The reason is not clear.

Summary

An attempt was made to trace the development of hepatic fibrosis of cardiac origin from the earliest to the latest phases. The earliest is that conventionally described in the "nutmeg" liver, and the prominent lesions are the dilatation of the central sinusoids with trabecular narrowing. Later, centrolobular necrosis ensues. Thereafter, the morphologic changes are entirely dependent upon whether a hypertension of the portal circulation is maintained over a sufficiently long period. This occurs usually in constrictive pericardium, and often in the terminal stages of tricuspid disease. The proof that portal hypertension is maintained was shown in the histologic demonstration of a "congestive splenomegaly" in every instance. Under such circumstances, various forms of fibrosis occur: first, capillary sclerosis around the central veins; second, organization of the centrolobular necrotic areas with the development of new central veins in these fibrotic areas, both by capillarization from the invading lymphocytes and by direct sprouts from the terminal branches of the portal vein in the interlobular septa; third, by sclerosis of the hepatic veins and the immediately adjacent parenchyma. The periportal fibrosis that has been described as occurring in "cardiac cirrhosis" is specious, and bears no resemblance to that observed in true Laennec's cirrhosis. Cardiac fibrosis is not a replacement fibrosis but is an active and proliferative process. Simultaneously, new capillary shunts or short circuits are developed. There are four kinds of such shunts: first, between the terminations of the portal vein in the interlobular septa and the central vein; second, by newly formed capillaries that bud from the terminal branches of the portal veins within the portal septa to the central veins; third, by budding from the preëxisting portal branches in the interlobular septa to the newly formed central veins, and fourth, by direct capillary communication between the terminations of the portal veins in the inter-

lobular septa and the hepatic veins. These shunts are viewed as compensatory mechanisms to help equalize the pressures between the portal vein and the hepatic veins. Evidence has been submitted that the morphologic changes of cardiac fibrosis are the result of portal hypertension of central origin. The clinical implications of cardiac fibrosis have been briefly summarized.

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DIVERTICULA OF THE GASTROINTESTINAL TRACT *

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The subject of diverticula and their attending complications is one which is usually without drama and therefore usually without great interest to the average physician. The great majority of cases are not diagnosed clinically but are discovered during surgical procedures or, what is more common, during an examination by the roentgenologist searching for some other condition. It has been stated that "the average practitioner still fails to recognize it as one of the daily recurrent important diseases, or to include the search for its diagnosis among his routine examinations." [1]

It is our hope that this review will reawaken an interest in the subject, for the clinical diagnosis is usually not too difficult if the possibility of the occurrence of the condition is kept in mind.

The cases in this report were seen in Butte by the authors. A total of 221 cases of diverticula of the gastrointestinal tract were seen in a four year period (1947–1950) during routine fluoroscopic examinations of the gastrointestinal tract by a roentgenologist (J. G. S.) and in clinical practice by an internist (M. A. G.). Approximately 4,900 cases were fluoroscoped. Of the 221 cases, 25 (11.3 per cent) were examined radiologically with a clinical diagnosis of diverticulosis or diverticulitis or both. The overall incidence of those having roentgen studies for gastrointestinal complaints was 4.5 per cent.

Our cases are divided anatomically as follows:

Esophageal	15
Stomach	1
Small Bowel	
Duodenum	64
Jejunum	1
Ileum	0
Meckel's Diverticulum	1
Large Bowel	139
Total	221

Each division will be discussed separately.

Diverticula of the Esophagus

Diverticula of the esophagus are classically divided into pulsion type, traction type and traction-pulsion type. They have been further classified into congenital or acquired groups, but the consensus seems to be that none are congenital, since they have never been reported in the newborn. King [2]

* Read at Montana-Wyoming Regional Meeting of American College of Physicians, Butte, Montana, October 6, 1951.

says he has no knowledge of the occurrence of a case prior to the age of 15 years.

Diverticula may occur in any portion of the esophagus but are most common in the middle third, next most common in the lower third, and least common in the upper third. However, there is variation of opinion as to the incidence in these locations.

Those diverticula occurring in the pharyngoesophageal region are practically all of the pulsion type. Their site of origin is at the junction of the pharynx and esophagus, at a congenital point of weakness bounded above by the lower fibers of the inferior constrictor muscle of the pharynx and below by the cricopharyngeal muscle. As a result of incoördination of those muscles in the act of swallowing whereby the cricopharyngeal muscle fails to relax, creating an obstruction below when the constrictors of the pharynx are contracted, pressure is directed posteriorly at the point of weakness, producing a bulge which, gradually advancing, thereby eventually becomes a diverticulum. The above is accepted by most authors as the etiology of this disease. There is, however, some difference of opinion as to whether the point of weakness mentioned above is congenital or acquired in origin. King [2] believes that there is no separate cricopharyngeal muscle. He is of the opinion that the muscle fibers involved are those of the inferior constrictor of the pharynx. These fibers develop an acquired weakness as a result of pressure between the ridge of the fifth cervical intervertebral joint and the lower border of the cricoid cartilage resting against this joint. Differences in stature and length of neck and variations in the anterior curvature of the cervical spine explain the lack of development of this condition in more individuals.

Coburn [3] believes that eating habits have some part in the production of these diverticula.

Poor mastication in an elderly individual with false teeth who is a rapid eater and who swallows large boluses of food may provide the pressure which produces outpouching at the site of a congenital defect if one is present.

Most reports indicate that these diverticula originate from the posterior wall of the esophagus and, as they enlarge, extend downward and to the left. However, Shallow and Clerf,[4] in an analysis of 186 operated cases, found that all but two originated from the left lateral wall of the esophagus. Their esophagoscopist reported 60 per cent of these cases as arising directly posteriorly. They explain this discrepancy on the basis that the diverticulum, when it enlarges and descends, produces a torsion of the esophagus, thereby making it appear to the esophagoscopist that it arose posteriorly. At operation, when the diverticulum is dissected free, correcting the torsion, it most often arises from the left side. No explanation is given for the greater frequency on the left side.

The walls of these diverticula usually consist of mucosa, submucosa and

a few strands of muscle fibers. Their size may vary from 0.5 to 8 cm. in their longest diameter.

Males are affected about three times as often as females, and the great majority of cases occur from the sixth decade on. Very few cases are seen under 40 years of age. Shallow and Clerf [4] in their series reported 82 per cent occurring during and after the sixth decade.

The classic symptoms of these diverticula are dysphagia and regurgitation of food and mucus. Other symptoms are gurgling, coughing, hoarseness, a sensation of strangulation, emaciation, dehydration and a feeling of fullness in the neck. The symptoms will of course vary with the size

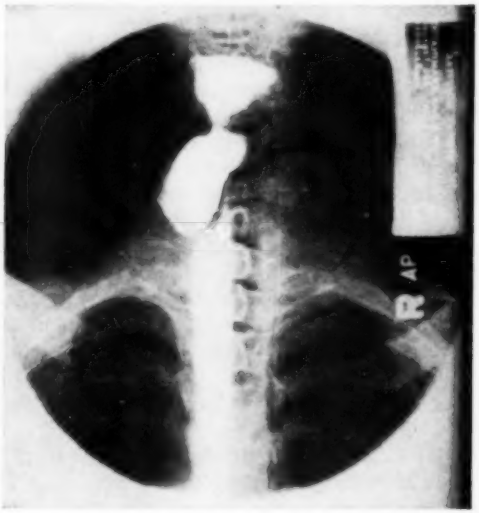

FIG. 1. This is an example of a moderately large pharyngoesophageal diverticulum in its most typical location on the left and extending downwards. The patient was a 62 year old woman who had had dysphagia and regurgitation of food for three years previously. She was subjected to operation and achieved a cure.

of the diverticulum. Dysphagia will vary from a temporary occasional lodging of a piece of dry food in the throat to almost complete obstruction. In the more severe degrees of dysphagia the obstruction is due to traction on the wall by the large, heavy, filled sac, producing marked distortion of the lumen of the esophagus.

Regurgitation of food and mucus may occur at varying times after eating. Not uncommonly, undigested pieces of food eaten one to three days previously are involuntarily discharged. Regurgitation occurs most commonly at night when the patient is lying down. Patients with large sacs may even be able to force out the contents by pressure on the neck.

Strange gurgling noises when swallowing are audible and embarrassing to many of these patients. Coughing and hoarseness are due to pressure on adjacent structures. Emaciation and dehydration occur when the sac reaches such size that it seriously interferes with swallowing. The duration of symptoms averages four and one-half years before the diagnosis is made, according to Shallow and Clerf.[4]

One of the commonest complications is inflammation, and in one series the esophagoscopist saw it in 77 per cent of cases.[4] Less common complications are perforation and formation of fistula.

The presence of this condition is strongly suggested by the symptoms. A few cases of small size are discovered incidentally. Roentgen examination and esophagoscopy are the positive means of diagnosis. The roentgen studies should be performed first, since in the case of a large diverticulum with distortion of the esophagus it is possible to produce a perforation of this sac if the esophagoscopist should blindly enter the structure and force his instrument through the wall, thus producing a mediastinitis. Fluoroscopic and roentgenographic studies should be made in both upright and recumbent positions and in all directions in order to outline completely the diverticulum, to determine whether it fills or empties readily, and to determine the size of the neck. Sometimes the consistency of the barium suspension may have to be varied since, if the opening is too small, it may not admit passage of too thick a mixture. The amount of barium administered should also be gauged fluoroscopically, as it may regurgitate into the trachea if too much is given. These diverticula are usually rounded or pear-shaped, with smooth walls. Retained food particles may give an irregular outline to the sac. Most of these sacs will retain barium for a considerable time.

Dilatation with bougies passed over a swallowed string is the only nonoperative method of treatment. It is only a temporary measure and is of no value in early or far advanced cases with almost complete obstruction. The only definitive treatment is surgical removal externally, or inversion. External surgical removal may be done in one or two stages. The two-stage method was developed to prevent the complication of a mediastinitis. However, with the advent of antibiotics, more surgeons are turning to the one-stage method without fear of complicating infection. The inversion method is "especially applicable to cases in which the patient is considered a poor risk and for use by the general surgeon who may occasionally treat such a case. It completely eliminates the complications that may arise from an open esophagus."[3]

Traction diverticula are the commonest type in the esophagus. They occur most frequently in the middle third on the anterior or lateral walls (figure 2). Most of these diverticula are single, although rarely they may be multiple. They usually do not reach the size of pulsion diverticula and may be triangular or globular in outline. Most of them are 1 to 2 cm. in

their greatest diameter. The opening into the esophageal lumen is usually so large that they fill and empty readily. It is almost universally accepted that they originate by traction at a localized position on the esophageal wall by an adjacent inflammatory lesion. Since most of them occur in the middle third, the inflammatory process usually arises in a lymph node in the region of the tracheal bifurcation or beginning of the main bronchus. By scarring and contraction, a pull is exerted on the adjacent, less resistant wall of the esophagus, thus creating the diverticulum. Often calcium may be seen deposited in the involved lymph node as a result of chronic inflammation.

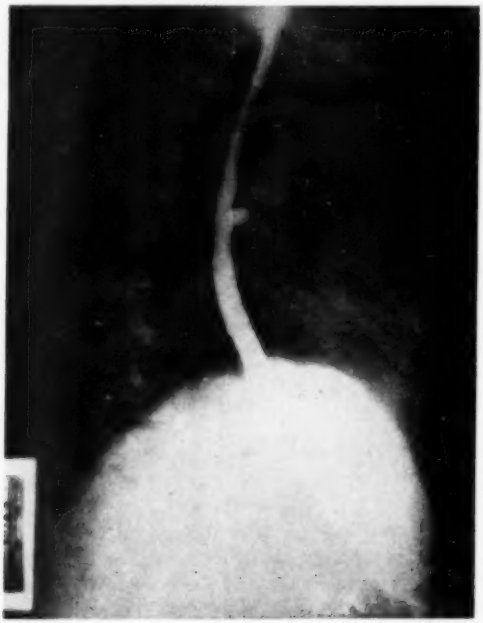

FIG. 2. Here is demonstrated a typical traction-type diverticulum involving the middle portion of the esophagus. The patient was a 55 year old male who had no symptoms referable to the esophagus. It was discovered incidentally during a routine gastrointestinal study.

The great majority of these diverticula are asymptomatic, but occasionally they cause dysphagia, a feeling of food sticking, or burning behind the sternum at the level of the diverticulum. A few cause mild regurgitation. It is surprising how patients with symptoms can point exactly toward the diverticulum as the location of their distress. It is difficult to explain why some of these may give rise to symptoms, and others of approximately the same size may not, even though they all fill and empty easily.

Uncommonly, traction diverticula may be complicated by perforation, ulceration and hemorrhage.

These diverticula are also seen mostly in older individuals, usually after 50 years of age.

Diagnosis is made in the same manner as with the pulsion type. Roentgen examination must be done more carefully when a traction diverticulum is suspected, because they are smaller, and the patient must be turned in all directions. Small diverticula may be obscured by the barium-filled esophagus if the patient is not rotated. Some may fill and empty so rapidly that they may be overlooked. Many of those without symptoms are discovered incidentally in the course of a routine gastrointestinal series.

In the lower esophagus they must be differentiated from an ulcer or a small hiatus hernia of the diaphragm containing stomach.

Treatment for cases with severe symptoms is surgical, usually with good results, and there should be no hesitation as to surgical intervention in such cases in these days of modern thoracic surgery. Nonsymptomatic diverticula are best let alone.

Traction-pulsion diverticula are merely a further stage of the above described traction type, where they are further dilated by intraesophageal pressure. This classification seems somewhat superfluous, since probably in case of all traction diverticula, both pressure and traction contribute to their increase in size.

In conclusion, it may be stated that diverticula of the esophagus are especially interesting from the roentgen standpoint. They should always be looked for in any gastrointestinal study, since their demonstration even if the patient is asymptomatic, may aid in diagnosis of a possible perforation or hemorrhage.

Diverticula of the Stomach

A study of reports of gastric diverticula in the literature indicates that they are very rare. The reported incidence roentgenologically varies from .04 to 0.64 per cent. Palmer,[5] in a recent very complete review of gastric diverticula in the literature, compiled statistics of 31 reports and found an incidence of .043 per cent in 380,099 routine gastrointestinal studies. In 1,371,000 general hospital admissions the percentage was .0043. They were found in 0.3 per cent of gastroscopic examinations. All told, he found 412 cases reported in the literature up to May, 1951. In June, 1951, Van Wezel [6] described another case. Bralow and Spellberg [7] reported 26 new cases of true diverticula in 1948 and indicated that this represented an incidence of 2.6 per cent in 350 gastroscopic examinations. It is difficult to account for this disparity in figures; however, this is the highest incidence we found reported, and perhaps their diagnostic acumen is sharper than most.

Diverticula of the stomach are usually classified as true, or congenital, and acquired, or false. In the true type the diverticulum is a primary

disease. The acquired type is secondary to some other extragastric or intragastric disease. It has not been proved that all true diverticula are necessarily congenital. Palmer [5] found 10 cases reported from birth to 10 years of age. True diverticula have walls made up of all the layers of the stomach. Seventy-five to 85 per cent of cases occur on the lesser curvature in its posterior aspect just below the junction of the esophagus and cardiac end of the stomach.

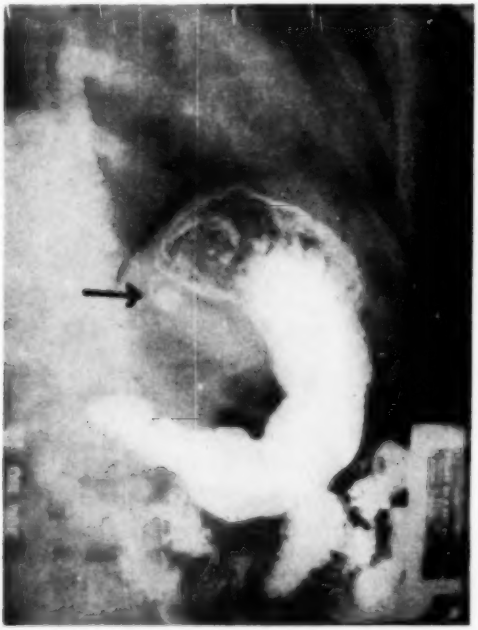

FIG. 3. Illustrated is a typical gastric diverticulum found during routine roentgen studies in a 25 year old woman. There were no symptoms referable to the stomach.

Acquired diverticula usually occur in the pyloric end of the stomach. As stated above, they result from some other primary disease, either intragastric or extragastric, by either a pulsion or a traction effect, or both.

The size of true diverticula varies from 1 to 6 cm. in diameter.

With regard to the symptomatology, it may be stated that there is nothing characteristic. In reading the literature one gets the impression that the great majority of cases are asymptomatic. However, Palmer,[5] in his review of 412 cases, found that 267 were discovered during a clinical study because of certain symptoms. In 148 of these cases he found the following rates of occurrence of these symptoms. Seventy-two patients

complained of epigastric or lower thoracic pain; 52 had complex dyspepsias; and the remainder presented themselves with typical symptoms of ulcer, vomiting, hematemesis and acute abdominal pain due to rupture. In the light of these figures, one should certainly consider these true diverticula as a possible cause of symptoms more often than has been done in the past.

Most diverticula are discovered roentgenologically. The stomach should always be examined in upright and supine positions, and the patient turned in all directions. There is usually no great difficulty in the roentgenologic differentiation of this condition. The majority of these lesions have a smooth, usually circular outline, with a narrow neck. They usually fill readily and, as stated previously, are found characteristically along the lesser curvature of the stomach on its posterior aspect just below the esophageal orifice into the stomach. They often will retain barium for from six to 24 hours, and in the upright position they may have a fluid level capped with air. The diverticulum may sometimes be outlined by air in the unfilled stomach. Mucosal folds are occasionally observed in the neck of the sac.

They are also diagnosed by gastroscopy, but the great majority are discovered by roentgen studies.

Uncommonly, gastric diverticula are complicated by inflammation. This may be suggested if there is tenderness over the diverticulum when palpable and if symptoms suggest it, or if there is irregularity in outline of the diverticulum.

Definitive treatment for a gastric diverticulum is surgical removal. If it is believed that the diverticulum is the cause of the patient's symptoms, it should be removed without hesitation. Medical treatment, including postural drainage, will often relieve symptoms, but it is not curative. Asymptomatic lesions are best let alone.

Diverticula of the Duodenum

Diverticula of the duodenum are, next to those of the large bowel, the most common in the gastrointestinal tract. The incidence in reported series varies greatly. Greenler and Curtis [8] averaged the figures in five reports and found 81 cases in 1,825 autopsies, giving a percentage of 4.4. They state that the incidence is much less by roentgenologic studies, inasmuch as only 1.4 per cent of the gastrointestinal examinations resulted in this diagnosis when seven reported series were averaged.

Most of the diverticula of the duodenum are discovered after the fourth decade, and there is no definite predilection for either sex.

They occur in any portion of the duodenum but are most common in the descending second portion on its concave side around the ampulla of Vater. About three-fourths occur in this area. The next most common site is the third portion of the duodenum, and then follow the first part and lastly the fourth part, or ascending duodenum (figure 4). They vary in size from 5 mm. to 6 cm.

Duodenal diverticula are commonly classified into the true and acquired, or pseudodiverticula. Many believe that true diverticula occur at points of weakness in the wall of the duodenum where blood vessels pass through the muscularis. Increased intraluminal pressure contributes to their production. Most of these diverticula occur on the side of blood supply to the duodenum, which is considered strong evidence in favor of this theory. Some consider them merely as anomalous outpouchings at a site in the intestines where outpouchings normally occur, such as in the formation of the biliary tract, liver and pancreas.

FIG. 4. Here are shown three diverticula in the fourth portion of the duodenum found in a woman 40 years old. This was a routine study and no symptoms could be definitely ascribed to these diverticula.

Diverticula of the acquired type are often called pseudodiverticula and are usually secondary to ulcers, surrounding inflammatory processes or adhesions. Most of those in the first portion of the duodenum are of this type and are usually secondary to peptic ulcers.

True diverticula may contain all the coats of the intestine in their wall, but if they become large the muscularis may become thinned and disappear. They are quite commonly single, but it is not uncommon to find multiple sacs—up to five or more.

It is generally agreed that the greater number of true diverticula are symptomless. Mahorner [9] believes that probably 98 per cent are asymptomatic. It is often difficult to decide whether duodenal diverticula are a cause of the symptoms in the abdomen with which the patient presents himself.

Mahorner [9] lists symptoms in the following order of occurrence: "Pain, nausea, vomiting, weight loss, diarrhea, jaundice, pancreatitis with its pain and other symptoms, and those of peritonitis due to perforation." There is no syndrome typical for symptomatic true diverticula. In a patient presenting himself with abdominal complaints, if nothing else can be found to account for them, one might have to decide that the diverticulum could be the cause. Since over 90 per cent of cases are considered as being clinically insignificant, and since the only cure is difficult—operation with some attending mortality—one must certainly be very careful before deciding that the diverticula, which are the only abnormality found on gastrointestinal examination, are the cause of the symptoms.

It is believed that symptoms are usually caused by complications such as inflammation, ulceration, hemorrhage and pressure on adjacent organs or ducts. Occasionally one is able to determine the presence of complications roentgenologically and thus to ascribe the symptoms definitely to the diverticula.[10, 11]

The diagnosis of duodenal diverticula is usually made roentgenologically. The examination, as always, should be done with the patient upright and supine and rotated. In this manner the diverticulum can be accurately localized. Attempts should be made to palpate it to determine how easily it fills and empties and whether tenderness is present. A diverticulum usually has a rounded, smooth, sac-like outline with a narrow neck connecting it to the duodenum. In the upright position it may present a fluid level with air above it. Occasionally it may be outlined by air without the presence of barium. It may retain barium for some time. Occasionally a diverticulum may not fill for some time. Rarely, an ulcer niche can be seen in the wall of the diverticulum. Irregularity in outline of a diverticulum, along with point tenderness over it, suggests the presence of diverticulitis. This may also cause spastic deformity of the portion of the duodenum to which the diverticulum is attached.

The only curative treatment is surgical removal in those cases thought to be causing symptoms. Cattel of the Lahey Clinic, in discussing Mahorner's [9] paper, stated that in that institution, in the 10 years from 1940 to 1949, 26 cases of duodenal diverticula were operated on, which represented 3 per cent of their cases of diverticula discovered by roentgen examination. His indications for surgery were persisting pain, persisting digestive symptoms and gastrointestinal hemorrhage. Most surgeons will probably agree with these indications if no other cause of symptoms can be found.[12] If a trial of medical treatment is desired, one may attempt a peptic ulcer régime.

Diverticula of the Small Intestine

Diverticula of the small bowel, excluding those of the duodenum and Meckel's diverticula, are very uncommon. They are the least common of these structures anywhere in the gastrointestinal tract.

The incidence of diverticula of the small intestine found by autopsy varies greatly in reports and is given as from .02 to 1.3 per cent. The roentgen incidence in roentgenologic examinations has been reported as being anywhere from .0004 to 3 per cent. Most authors do agree, however, that their occurrence is very low. Williams and Walker [13] claim to have found 300 cases reported in the literature up to the time they added two more cases to this number in 1946. They occur about evenly between the two sexes. Most cases are found after the age of 40 years, and the greatest number are seen in the seventies.

The classification of diverticula of the small bowel is most commonly given as true, or congenital, and false, or acquired. Meckel's diverticulum is in the congenital group; and the remainder are in the acquired group. Meckel's diverticulum has a definite known congenital origin from the vitelline duct. The remainder of diverticula of the small bowel do not have a definitely proved origin. Consequently, King [14] believes that the above classification is meaningless, and he thinks it more logical to classify diverticula into antenatal and postnatal types.

Diverticula of the small bowel are most common in the upper jejunum (figure 5) and least common in the ileum. They may be single or multiple. The majority of reports indicate that they usually are multiple. They are usually rounded and vary in size from a few millimeters to several centimeters. Most of these diverticula are found along or adjacent to the mesenteric border of the bowel. They may project into the mesentery, separating its layers, or may protrude to the side of the mesentery.

The location of these diverticula furnishes the basis for the theory that they result from a pulsion effect at the site of weakness where the mesenteric vessels penetrate the wall of the small bowel. This produces a herniation of the mucous membrane through the muscularis. Fraser [15] experimentally produced outpouchings of the jejunum in postmortem specimens by introducing bismuth solutions and oxygen under pressure into the bowel and demonstrated these outpouchings along the mesentery at the site of penetration of an artery. He believed this confirmed the above theory, which is accepted by most authors. However, King [14] does not agree with this theory. He finds that many of the smaller diverticula have muscle fibers in their wall, and if they all represented herniations of the mucosa through the muscularis, none should have muscle structures in their walls. He believes that they, as well as diverticula in other locations, are the result of a general tissue weakness, and the presence of the blood vessels with each diverticulum represents only an incidental phenomenon and has no relation-

ship to their production. The weakness represents a degeneration of the muscular tissues.

The walls of diverticula vary a great deal. Many authors agree that the smaller ones have all coats of the intestines in their walls, while larger ones may have only mucosa and submucosa in their walls.

There is nothing characteristic about the symptoms of diverticula of the small bowel. The great majority are discovered incidentally during roentgenologic examination for some other condition. Jejunal diverticula may be unaccompanied by clinical symptoms.[16] Probably most cases do not

FIG. 5. The arrows point to two small diverticula involving the upper jejunum. The patient was a 45 year old woman with no symptoms referable to the diverticula.

produce symptoms, but those that do are complicated ones. When diverticula are found with other conditions, such as peptic ulcer, biliary disease or other lesions, it is difficult to determine whether they are symptomatic. Ritvo and Votta [17] state that diverticula may cause mild, chronic abdominal pain, soreness, gaseous distress, or severe epigastric distress with nausea and vomiting. They indicate that the symptoms are intermittent, with no relationship to meals, bowel movements or exertion. Abdominal cramps may occur. It is believed that such symptoms are due to inflammatory changes in the diverticula or around them. The sacs may become full of

intestinal contents and distended and not empty readily. Intestinal concretions may occur in them. Occasionally these structures perforate, giving rise to acute symptoms of a ruptured, hollow viscus. They may become ulcerated and produce hemorrhage, a not uncommon complication. Traction on the bowel or pressure by large diverticula may produce intestinal obstruction, chronic or intermittent in type.[18]

Roentgenologic examination is essential for diagnosis, although many diverticula are probably overlooked.[19] A plain scout film of the abdomen may reveal diverticula if they are filled with gas. The great majority must be studied by orally administered barium or intestinal intubation. If diverticula are found, the patient should be studied fluoroscopically to elicit point tenderness or disturbance in intestinal function. Studies should be made at frequent intervals following the barium meal, since many of these diverticula may empty rapidly and be missed if only a routine follow-up film is made at five to six hours. Roentgen examination is contraindicated in the presence of acute inflammation.

Just as with duodenal diverticula, one must be reasonably certain that jejunal or ileal diverticula, if found, are a cause of the symptoms. The only curative treatment is surgical, and there should be no hesitation to resort to operation if one can rule out all other causes of the patient's symptoms. Medical treatment, in the form of a low residue diet, medication and postural drainage, has been used, but this does not remove the diverticula and will not necessarily prevent complications which may require emergency abdominal surgery.

Meckel's Diverticulum

Meckel's diverticulum is a congenital anomaly which results from the failure of the omphalomesenteric duct to close. This omphalomesenteric duct, which connects the yolk sac with the primitive intestine, begins to be obliterated in from the third to the fifth week of fetal life, and this is usually complete by the seventh week. Various degrees of failure of obliteration lead to several grades of maldevelopment.[20] If the entire duct remains open, this results in a fecal fistula opening at the umbilicus. Failure of the distal end to close will result in an intestinal fistula opening at the umbilicus. Closure of the ends and persistence of the midsection will result in a retention cyst. Failure of the proximal end to close forms an outpouching of the intestinal tract, usually at the terminal portion of the ileum, producing Meckel's diverticulum. Occasionally there is persistence of a fibrous stalk or cord connecting the tip of the diverticulum with the inner aspect of the anterior abdominal wall near the umbilicus.

Meckel's diverticula are found in the terminal ileum 15 to 100 cm. from the ileocecal valve and usually projecting from the free border of the ileum. Their shape is variable, as is their size, which may vary from that of a small vestigial nubbin, 2.5 mm., to one as large as that reported by Moll [21]

which measured 33.5 inches (850 cm.). A mesentery like that of an appendix may be present.

It is quite common, occurring in approximately 2 per cent of all persons,[22] and more frequently in males than in females.

Meckel's diverticulum contains all the coats of the bowel. One of the most interesting features is the presence of heterotopic tissue, which may occur in 25 per cent of all diverticula.[23] Of the cases producing symptoms, this incidence may rise to 60 or 75 per cent.[24] The most common type of heterotopic tissue is gastric mucosa, and this is followed in incidence by duodenal and pancreatic tissue, although biliary, ileal, jejunal and colonic mucosa may also be found.[25] The gastric mucosa is capable of secreting hydrochloric acid and pepsin, which may produce erosions and ulceration, bleeding and perforation.[26]

Greenblatt et al.[27] have classified the pathologic conditions which occur in Meckel's diverticulum as follows:

1. Peptic ulcer type
   - *a.* Gastric mucosa without ulceration
   - *b.* Gastric mucosa with ulceration
   - *c.* Ulceration with hemorrhage
   - *d.* Ulceration without hemorrhage
2. Obstruction type
   - *a.* Intussusception
   - *b.* Volvulus
   - *c.* Congenital bands and adhesions
   - *d.* Contents of hernia
3. Diverticular type
   - *a.* Simple acute inflammation
   - *b.* Perforated and gangrenous
   - *c.* Chronic inflammation
4. Umbilical type
   - *a.* Fecal fistula
   - *b.* Umbilical adenoma
   - *c.* Prolapsed intestine through fistula
5. Tumor type
   - *a.* Benign
     1. Carcinoid
     2. Enterocystoma
     3. Adenoma
     4. Mesodermal tumor
   - *b.* Malignant
     1. Carcinoma
     2. Sarcoma

c. Heterotopic
   1. Pancreatic
   2. Gastric
   3. Biliary
   4. Colonic
   5. Jejunal
   6. Duodenal

6. Incidental type
   a. Normal picture of ileum

The symptoms of Meckel's diverticulum are not typical or characteristic but are dependent upon the developmental deformities present. The most common are a result of obstruction, inflammation, or ulceration.

Obstruction due to a Meckel's diverticulum gives the same clinical picture as that due to obstruction or intussusception from other causes. The exciting factor of intussusception caused by a Meckel's diverticulum is usually a nodule of pancreatic tissue situated near the fundus of the diverticulum.[28] The symptoms of inflammation of a Meckel's diverticulum usually resemble attacks of appendicitis.

When ulceration occurs it is usually due to the presence of heterotopic tissue, and it produces a clinical picture similar to gastroduodenal ulceration, with its attending complications. The ulceration is usually at the base, at the junction of the intestinal mucosa, and has been compared to the marginal ulcer which develops after gastroenterostomy.[29] Intestinal hemorrhage, which may be massive, may be a very significant finding.

The demonstration of a Meckel's diverticulum roentgenologically is a rarity.[29] The reason for this is that they are probably obscured by the overlying small bowel. Bockus [30] recommends very frequent films, exposed with the patient in all the positions necessary to demonstrate a diverticulum. Calculi may be demonstrated in the diverticulum, although this is very rare.[31, 32]

The correct preoperative diagnosis is rarely made, since all the symptoms may occur as a result of other intraabdominal disease. However, the condition should always be suspected in the presence of melena of undetermined origin, particularly in children.

The treatment is surgical and is directed toward relieving the symptoms produced by the diverticulum, and it should include excision of the diverticulum. All cases found incidentally during other surgical procedures should be removed, if the patient's condition permits, because of the possibility of complications.

Diverticula of the Colon

There is no unanimity of opinion as to the causative factor or factors that produce diverticula of the colon.[33] Some of the theories of etiology

discussed by Williams and Williams [34] include congenital malformation, constipation with increase of gaseous pressure, degenerative changes due to old age, inherent weakness of the colon wall, excessive obesity or sometimes emaciation, and disturbance of the sympathetic nervous system controlling the part.

Bacon and Sherman [35] feel that the most tenable theory is that diverticula are due to herniation of intestinal mucosa near points of entry and exit of blood vessels. Fansler's [36] opinion is that diverticula develop in the

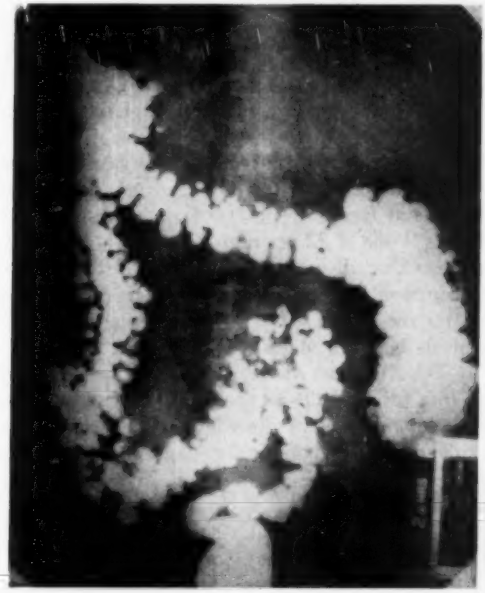

FIG. 6. Illustrated are multiple diverticula involving the entire colon, with evidence of diverticulitis in the lower descending and sigmoid colon. The patient, a female aged 65 years, gave a history of recurring pains in the left lower abdomen, constipation and occasional hemorrhage of red blood.

haustra of the colon, the wall of which has only one layer of circular muscle. In these haustra the susceptibility of the muscular wall to stretching and thinning is increased, especially where the intestinal tension is greatest. This stretching and thinning in elderly individuals may result in herniation and diverticula.

The development of diverticula is usually explained on the basis of a muscular deficiency occurring usually during the years of degenerative changes in the body.[37] It is generally agreed that diverticulitis results from

improper emptying of the diverticulum. The increased incidence of diverticulitis of the sigmoid has been explained by Smithwick [38] on the basis of the narrow lumen, stasis and solid fecal material in this portion of the large bowel. The factors of the propulsive mechanism of this segment and its tendency to spasm have been added by Mayo and Blunt.[39]

Diverticulosis is found in approximately 5 per cent of individuals having symptoms referable to the large bowel.[40] An incidence of 8.5 per cent in patients requiring roentgenologic examination of the colon has been reported by Pemberton [41] et al. Approximately 80 per cent of diverticula are located in the sigmoid. The rectum is rarely involved, and the incidence decreases steadily between the sigmoid and cecum. Mayo's [42] figures are even higher for diverticulitis. In a report of 202 cases of diverticulitis of the colon, 198 (98 per cent) were found in the sigmoid, one (0.5 per cent) each in the descending and transverse colon, and two (1 per cent) in the cecum.

Diverticulitis occurs at some time in approximately 20 per cent of cases of diverticulosis. Rankin and Brown [40] reported the incidence to be 17 per cent. Ochsner and Bargen [43] observed an incidence of 27 per cent and Willard and Bockus [44] one of 22 per cent.

Bearse [45] believes that diverticulosis occurs more frequently in younger persons than is commonly accepted. Most observers consider them to become manifest after the age of 40.[46] There seems to be an equal distribution of diverticulosis between males and females.

It is usually believed that diverticulosis is symptomless. Maingot,[47] however, feels that diverticulosis produces symptoms which are mild, amounting to little more than a disordered action of the bowel, such as intermittent flatulence, slight abdominal distention and occasional uneasiness or mild spasm along the course of the colon, and more particularly in the left iliac fossa. But genuine pain and the symptoms usually associated with inflammation of a hollow abdominal viscus are conspicuously absent, and signs apart from the radiological findings are lacking.

Lynch [48] also believes that all people with diverticulosis have symptoms, but the symptoms are overlooked and are considered due to dietary indiscretions and the like. He feels that there is always dull aching pain accompanied by occasional attacks of diarrhea, alternating with constipation and gaseous distention. This opinion is contrary to that of the majority of observers, who feel that some degree of inflammation must be present to produce these symptoms, and that the condition is then one of diverticulitis.

The classic picture of diverticulitis includes pain in the left lower quadrant, low grade fever, slight leukocytosis, some nausea and irregular bowel habits, but not all of these symptoms need be present.[49] Two symptoms which should receive more consideration are pain in the back and melena. LeRoyer and White [50] have found that the complaint of pain in the lower

back occurred in 20.5 per cent of their cases. Another symptom, which they felt may often be the presenting complaint, is the passage of blood by rectum, either as free blood or as flecks on the fecal material. Morton [51] found this complaint in 32 per cent of his patients.

Diverticulitis may be found in a variety of forms. The following outline, from Bockus,[52] gives one an idea as to the multiple conditions which may arise:

I. Acute Diverticulitis
  A. Simple
  B. Complicated
    1. Rupture of inflamed diverticulum
      a. Into free peritoneal cavity
      b. Formes frustes with plastering
    2. Peridiverticulitis
      a. Simple
      b. Enterospasm
        1. Without obstruction
        2. With acute obstruction
          a. Partial
          b. Total
        3. With chronic obstruction
    3. Peritonitis
      a. Local
        1. Nonsuppurative
        2. With abscess
          a. Perforation
            1. General peritonitis
            2. Fistulas, single or multiple
              a. Enterointestinal
              b. Enterovesical
              c. Enterocutaneous
          b. General
    4. Resulting from lodgment of foreign body
    5. Metastatic suppuration
      a. Septicemia
      b. Suppurative pylephlebitis or portal pyemia
      c. As a focus of infection
II. Recurrent Diverticulitis
III. Chronic Diverticulitis
  A. Simple
  B. Complicated
    1. Peridiverticulitis
      a. Enterospasm
      b. Hyperplasia with obstruction

2. Mesenteritis
3. Peritonitis
   a. Acute
   b. Recurrent
   c. Chronic
      1. Adhesions
         a. With or without angulation and obstruction

Simple acute diverticulitis may occur in any portion of the colon but, due to the predominance of diverticula in the sigmoid colon, occurs most commonly in that area. It is frequently called "left sided appendicitis," because the signs and symptoms may resemble acute appendicitis. It varies considerably in intensity, some cases being mild while others may have marked local and constitutional signs and symptoms. They may have nausea and vomiting, localized pain in the left lower quadrant, constipation, elevated pulse rate, elevated temperature, leukocytosis, and tenderness and rigidity in the left iliac fossa. The symptoms may persist for a few days, followed by resolution, or the process may continue and one or more of the complications may follow.

Perforation of the inflamed diverticulum may occur but is relatively rare. Hayden [53] reported three instances in 140 surgically treated cases. The signs and symptoms include shock, generalized abdominal pain, a rigid, silent abdomen, and a rising leukocyte count. More commonly the perforation is of the formes frustes type, the small perforation is rapidly sealed off by omentum and intestines, and the signs and symptoms are less severe.

In cases of acute diverticulitis, there is usually an associated peridiverticulitis with enterospasm, colicky pains, disturbed bowel function with flatulence, constipation or diarrhea. As the process progresses, partial or total intestinal obstruction may occur.

Local peritonitis commonly appears with acute diverticulitis. The amount of reaction will depend upon whether there is a purulent response with abscess formation. The abscess may rupture into a hollow viscus, or into the general peritoneal cavity, or it may burrow to the skin surface.

Recurrent diverticulitis almost always indicates the presence of some complication.

"The phase of diverticulitis of the greatest clinical importance is the quiet, slow, inflammatory thickening of the intestinal wall, which ends by causing intestinal obstruction and so gives an almost perfect imitation of cancer." [54] Boyden [55] has reported three cases in which the diagnosis of carcinoma could not be ruled out prior to pathologic examination. Roentgen evidence of carcinoma was found in two cases. At operation, the lesions appeared grossly malignant, but carcinoma was not found by the pathologist.

The obstruction in chronic diverticulitis is of slow onset, rarely becomes absolute and is usually due to stenosing peridiverticulitis. The affected segment becomes hard and contracted into a rigid tube, and as a result of

edema of the mucous membrane a block may occur; in other cases, a mass may form.

In summary, the symptoms become consistent with the complications that develop. A sudden, acute pain in the abdomen suggests acute perforation with peritonitis; a mass in the left lower quadrant indicates an indurated, thickened sigmoid or a localized abscess; obstipation may mean inflammatory and fibrotic closure of the sigmoid; sudden disappearance of a mass, relief of pain and the appearance of pus from the urethra or rectum suggest perforation of an abscess with formation of a fistula. The symptoms and signs vary in direct proportion to the severity and extent of the inflammatory process.[56]

In most cases, radiographic study is all that is necessary for the diagnosis of diverticulitis.[57] The radiologic appearance of diverticulitis has been concisely described by Maingot.[47] The earliest suggestive finding of diverticula of the colon is an irregularity of haustra in a spastic type of bowel. The earliest positive finding is pinhead elevation on the surface of the bowel. The next stage is the "saw-edge" appearance. At a still later stage, a series of pear- or flask-shaped protrusions is seen, while the stage may be called advanced when the diverticula look like little spheres attached to the bowel by slender stalks. Henderson [58] describes the five stages observed on roentgenologic examinations as ripple border, pallisading, pulsion diverticula, retractable ballooning, and permanent diverticula.

The diagnosis is based on the history, physical examination, proctoscopy, and a barium enema study, the last being the most valuable and accurate procedure. All believe that roentgenologic examination of the colon is the greatest single aid in the diagnosis of diverticulosis and diverticulitis.

Usually the diagnosis of diverticulitis presents no problem if it is thought of, but there are certain times when it is difficult to make. The conditions most often confused with diverticulitis are appendicitis, carcinoma of the sigmoid colon, and masses involving the structures of the genitourinary tract. Acute diverticulitis in a cecal diverticulum or in a loop of redundant sigmoid colon which lies to the right of the umbilicus may cause this condition to be confused with appendicitis.

When carcinoma of the colon becomes a differential problem in diverticulitis, the clinical diagnosis may be impossible even under direct observation at operation. The final diagnosis in this type of case usually is made by the pathologist. It is believed that the two conditions may exist coincidentally and that carcinoma of the sigmoid rarely, if ever, develops from a preëxisting diverticulosis.

Occasionally the primary complaints of the patient may be dysuria, frequency and burning on urination. These symptoms may be accounted for by pressure on the urinary bladder by an inflammatory mass, which may in turn be attributed to neoplasm.

The prognosis in uncomplicated cases of diverticulosis is excellent.

Kocour [46] found six patients whose death was due to some complication of diverticulitis among 127 cases of colonic diverticula, an incidence of 4 per cent. In Maingot's [47] experience, about 10 per cent of cases of diverticulitis will develop complications of such a serious nature as to require operation.

The prognosis depends principally upon the stage of the disease, the complications and the type of treatment.

The management of the patient with diverticular disease varies with the type of involvement. Basically, the treatment is medical, with surgery reserved for cases with complications. Diverticulosis requires no active treatment as such. The treatment is based on the prevention of complications. A bland, nonirritating diet with low residue, free of fruits containing seeds and rough, stringy vegetables, is given. Correction of any associated disturbance of bowel habits is undertaken. Cases of mild diverticulitis, uncomplicated, should be given bed-rest, mineral oil at bedtime, antispasmodics, heat locally to the abdomen, and no solid foods until the stage of convalescence is reached.

Jones [59] states that he knows of no abdominal ailment which calls for more individualization or taxes our surgical ingenuity more than diverticulitis and its complications.

Maingot [47] believes that recurrent exacerbation of inflammation, the onset of bladder symptoms, or the symptoms of low grade obstruction of the large bowel are not genuine indications for operative interference. He feels that these are to be regarded as urgent pleas for more intensive and perhaps more efficient methods of medical management.

The indications for operation are the complications of diverticulitis, namely: perforation, abscess formation, obstruction and fistula formation. The method of treatment of each of these complications will be left to the judgment of the attending surgeon, and from the voluminous literature, his task is not an easy one! As a matter of record, the simplest procedure possible is accompanied by the lowest mortality.

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THE PROVOCATIVE SEROLOGICAL REACTION IN LATE SYPHILIS: ITS RELATION TO TECHNICAL FACTORS *

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With the simplification of treatment as the result of the demonstrated efficacy of penicillin, the major problem in clinical syphilis at the present time is the differentiation of positive serologic tests due to syphilis from those due to biologic false-positive reactions. The occurrence of "acute" or short-lived false-positive reactions following certain diseases and conditions such as malaria, infectious mononucleosis, viral pneumonia, smallpox vaccination and many others is well known. Ordinarily, false-positive reactions due to these causes revert spontaneously to negative in periods of days, weeks or, at most, a few months. In addition, it has long been suspected that "chronic" persistent false-positive reactions may occur, but the inciting agents and the conditions under which these reactions take place are less well defined. Under these circumstances, the significance of repeatedly positive serologic tests for syphilis in patients without historical, clinical or epidemiologic evidence of syphilitic infection, and in the absence of the recognized occurrence of diseases and conditions known to cause or suspected of causing false positive reactions, is frequently obscure.

In consequence, efforts have been made to differentiate positive tests due to syphilis from those due to false-positive reactions by serologic methods. Included among these attempts have been the Kahn "verification" test,[1] based in part on the temperature and salt concentrations under which the sera react; the Rein special technic,[2] which utilized the observation that the addition of unheated serum inhibited the flocculation of syphilitic but not of false-positive sera, and complement-fixation tests, using cultured (non-pathogenic) spirochetes.[3] It has been shown that, unfortunately, the results of these tests tend to reflect the height of the quantitative titer rather than serving to provide information of value in differentiating syphilitic infection from false-positive reaction.[2] The isolation of cardiolipin [4] and its employment as antigen in serologic tests for syphilis initially offered promise of being of differential value, but the results have not been encouraging. Two recent and as yet experimental technics do offer hope in this differentiation. The euglobulin-inhibition test developed by Neurath and his co-workers [5] has shown a high index of reliability except in patients with primary syphilis. Perhaps even more specific on the basis of preliminary reports is the trep-

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onemal immobilization test of Nelson and Mayer.[6] With this technic, the presence has been demonstrated of an antibody distinct from reagin which renders virulent *T. pallidum* nonmotile. Thus far, both of these newer tests are in the experimental stage and neither is available for clinical application.

Another procedure which has been advocated from time to time is the provocative serologic reaction. Since the original description of the phenomenon, reported independently by Milian and by Gennerich [7] in 1910, the validity of this procedure has remained controversial. The essential feature of this concept is that the injection of an antitreponemal agent into patients with late syphilis will result in a measurable increase in circulating syphilitic reagin. This procedure has been recommended, therefore, as an aid in the diagnosis of syphilis when serologic tests have been negative, doubtful, conflicting, fluctuating or otherwise inconclusive.

Although Krefting [8] and Pollitzer and Spiegel [9] early were doubtful as to the value of the procedure, others, including Stokes and O'Leary [10] and Lyons,[11] considered it worth while. Eagle [12] in 1937 stated that the provocative phenomenon could be demonstrated in more than one-third of previously untreated patients, but subsequently,[13] citing unpublished studies, he expressed doubt as to the existence of the provocative reaction.

Meanwhile, in 1935, Barnett, Jones, and Kulchar,[14] utilizing a technic especially designed to detect small amounts of circulating reagin, demonstrated the presence of minute quantities in normal nonsyphilitic persons, and subsequently (1938) these authors reported [15] that the reagin content in both normal and syphilitic patients increased after an injection of neoarsphenamine. It was their opinion, therefore, that provocative testing was unreliable, since the phenomenon could be demonstrated in nonsyphilitic as well as in syphilitic patients.

It has been recognized for many years that the reagin content of the serum of patients with treated late (and therefore presumably inactive) syphilis may show considerable variation from day to day when measured quantitatively. In 1940, Mohr and Smith [16] presented evidence that this apparent daily variation in reagin titer was due not to variations in amount of circulating reagin but instead to daily fluctuations in laboratory sensitivity of the tests. In this study, specimens of serum were collected at intervals of from one to three weeks over a period of several months. Quantitative titers performed on the day of bleeding were compared with those performed on the same sera preserved by freezing, and later were tested simultaneously. Although there was rather wide variation in the titers performed as the sera were obtained from day to day, when these sera were frozen and subsequently tested at the same time the titers remained essentially constant.

In spite of the divergent viewpoints expressed above, standard textbooks of syphilology continue to describe the provocative serologic reaction and to discuss indications for its use. For example, Stokes, Beerman, and Ingraham (1944),[17] although not indicating unqualified approval of the

provocative procedure because of expense, fear of therapeutic shock, fluctuation of serologic tests, etc., nonetheless state: ". . . There is sufficient accumulated evidence from Gennerich in 1910 to current experience to indicate that a rise in reagin titer both in the blood and spinal fluid does follow the use of antisyphilitic treatment in syphilitic persons, and that this may have some confirmative value in the more complex groups of procedures required for diagnosis in doubtful cases."

Kampmeier (1944) [18] concludes a discussion of the provocative test with the opinion that ". . . only rarely can the results be expected to be so clear-cut as to warrant an unquestionable serologic diagnosis of syphilis."

Kolmer (1949) [19] continues to endorse the use of the provocative reaction, although warning that the results may be negative more often than positive. He states: ". . . (The) provocative reaction is sometimes of value in the diagnosis of a previously untreated patient and especially when negative serum reactions are observed in the presence of a lesion thought to be syphilitic, or if weakly positive reactions are observed in the absence of suspicious lesions."

Despite the reservations expressed, the inclusion of a discussion of the provocative test by present day authors of standard texts implies at least a partial endorsement of the procedure.

The present study was undertaken to determine whether a provocative serologic reaction could be demonstrated under controlled conditions in patients with proved late syphilis and whether, therefore, this test might offer some assistance to the physician in the diagnosis of syphilis. The results of provocative testing have been studied in 12 patients with untreated late syphilis, employing three antitreponemal agents—Mapharsen (oxophenarsine hydrochloride), bismuth (both an oil-suspension and a water-soluble preparation), and procaine penicillin in oil.

Materials and Method

Since provocative testing has been recommended particularly in patients with untreated late syphilis, only patients in this category were selected for study. Because of the relative scarcity of patients with proved late syphilis other than neurosyphilis, a majority of the patients included were of this type.

A complete medical history, physical examination, preliminary blood serologic tests and an examination of the cerebrospinal fluid were performed prior to administration of the provocative agents. Two to four quantitative serologic tests for syphilis were obtained at varying intervals before treatment for base-line observations. In nine patients, the initial provocative agent employed was Mapharsen, administered in a dosage of 0.001 gm. per kilogram of body weight (maximum, 0.08 gm.). Serum for quantitative serologic tests was obtained on each of three or four days during the first week after the administration of Mapharsen (days 2, 4 and 7; or 1, 3, 5 and

7). Subsequently bismuth, either the subsalicylate suspended in oil (four patients) or a water-soluble preparation, Thiobismol (five patients), was injected once weekly for two to four doses, serum for quantitative serologic tests being obtained before each injection. In three patients, procaine penicillin in oil * (600,000 units) was the only provocative agent employed.

Thus, serum was obtained for titration approximately every other day during the first week after administration of the initial provocative agent (Mapharsen or procaine penicillin in oil), and at weekly intervals thereafter for three or more weeks. At the time of bleeding, double portions of blood were obtained, one portion of which was submitted to the laboratory immediately. The second portion was allowed to stand for from two to 18 hours until the clot had contracted; the serum was separated and then rapidly frozen in a dry-ice box at —70° C. In accordance with the method of Mohr and Smith,[16] the frozen specimens from each patient were allowed to accumulate until all specimens had been obtained. Thereupon, all frozen specimens from each patient were thawed simultaneously in a water bath at 37° C. and submitted to the laboratory. To guard against possible deterioration of the sera, serologic testing was performed on the day these specimens were submitted.

Two quantitative serologic tests for syphilis, Kahn and cardiolipin, were routinely performed on each serum specimen (fresh and preserved by freezing). With the quantitative Kahn procedure (test-tube technic), titration was performed as follows: undiluted, 1:5 dilution, 1:10, 1:20, etc. The cardiolipin test employed was a slide technic using V.D.R.L.† antigen and, for quantitation, serial two-fold dilutions were made: undiluted, 1:2 dilution, 1:4, 1:8, etc. With each technic, titers were expressed in terms of the highest dilution showing a positive result. These are the routine technics performed in the serologic laboratory of the Barnes Hospital.‡ Since one of the objectives of this study was to determine the practicability of the procedure, nonstandard refinements in technic, such as the utilization of intermediate dilutions, were purposely avoided.

Results

The results of provocative testing are presented individually for each patient. Brief clinical summaries precede the description of the result; detailed data on four patients are recorded separately in tabular form.

Case Reports

Case 1. This patient was a 34 year old Negro woman who had clinically latent syphilis of at least 17 years' duration. The initial blood serologic test was reported

* Duracillin in oil, Lilly.

† Venereal Disease Research Laboratory.

‡ The serologic tests for syphilis were performed through the courtesy of Dr. G. J. Dammin, Director of Laboratories, Barnes Hospital.

as Kahn positive in a 1:10 dilution,* cardiolipin positive in undiluted serum only. The cerebrospinal fluid contained 214/3 cells † (Fuchs-Rosenthal counting chamber), total protein = 60 mg. per cent, quantitative complement-fixation test for syphilis (Kolmer) positive in from 1.0 c.c. to 0.06 c.c. of spinal fluid; colloidal gold test = 5543321000. The diagnosis, therefore, was late asymptomatic neurosyphilis.

After three preliminary blood serologic tests for baseline observations (table 1) had been obtained, the initial presumably provocative agent employed was Mapharsen in a total dosage 0.08 gm. Blood for serologic testing was drawn on the second and third post-treatment days. Single injections of bismuth subsalicylate (0.2 gm.) were then administered on the third and tenth days, and further blood was obtained on the tenth and seventeenth days. Quantitative serologic tests for syphilis showed no significant change. On the sera submitted to the laboratory on the day of venipuncture, i.e., fresh sera, the reports of the Kahn test varied from positive in a dilution of 1:10

TABLE 1

Results of Titered Serologic Tests for Syphilis Performed on Fresh and on Preserved Sera in Case 1
Late asymptomatic neurosyphilis*

Days	Provocative Agent	Kahn		Cardiolipin	
		Fresh Sera	Frozen Sera	Fresh Sera	Frozen Sera
−28		1–10		Undil.	
−4		1–10	1–5	1–2	Undil.
0	Maph. 0.08 gm.	1–10	1–5	1–2	Dbt.
+2		1–10	1–5	Undil.	Dbt.
+3	Bi. Sub. 0.2 gm.	1–5	1–5	Undil.	Dbt.
+10	Bi. Sub. 0.2 gm.	1–10	1–5	1–2	Dbt.
+17		Undil.	1–5	Undil.	Dbt.
Range of Variation		Undil. to 1–10	1–5	Undil. to 1–2	Dbt. to Undil.
Dilution Difference		2	0	1	1

* With the Kahn test, titration was performed as follows: undiluted, 1:5, 1:10, 1:20, etc. With the cardiolipin test (V.D.R.L. antigen) serial two-fold dilutions were made: undiluted, 1:2, 1:4, 1:8, etc. Titers are expressed in terms of the highest dilution showing a positive result. Undiluted = positive in undiluted serum only. Dbt. = doubtful in undiluted serum. Blank spaces indicate that test was not performed on this date. Dilution difference = no. dilutions between the highest and lowest titer.

to positive in undiluted serum only. With cardiolipin, the variation was from positive in undiluted serum only, to positive in a 1:2 dilution. With the sera preserved by freezing, the Kahn was positive in a 1:5 dilution in all specimens, while the cardiolipin result varied only from positive to doubtful in undiluted serum. As is clearly demonstrated in table 1, no evidence of a provocative serologic reaction was obtained.

Case 2. This 50 year old white woman had syphilis of approximately 20 years' duration. On physical examination an early diastolic murmur was audible over the aortic area. The initial blood serologic test was reported as Kahn positive in a 1:40 dilution, cardiolipin positive, 1:32. The cerebrospinal fluid contained 649/3 cells, total protein = 110 mg. per cent, quantitative complement-fixation test positive in from 1.0 c.c. to 0.03 c.c. of spinal fluid, colloidal test = 5555321000. The diagnosis

* This is not the usual manner of reporting the results of quantitative Kahn tests, i.e., in "Kahn units," but as the highest dilution giving a positive result.

† 214 cells in 3.2 mm.^{3} of spinal fluid.

was cardiovascular syphilis with aortic regurgitation and late asymptomatic neurosyphilis.

After obtaining four preliminary quantitative blood serologic tests, the provocative agent used was procaine penicillin in oil, administered in a dosage of 600,000 units twice weekly. As recorded in table 2, the results on fresh serum were variable, the range of positivity with the Kahn technic being from a dilution of 1:20 to 1:60, and with cardiolipin from 1:8 to 1:32. With sera preserved by freezing, the results of the Kahn test varied only from 1:30 to 1:40, while all sera tested with cardiolipin were positive in a 1:16 dilution. There was no evidence of a provocative effect following the initiation of antisyphilitic treatment with this penicillin preparation.

Case 3. This patient was a 49 year old Negro man whose syphilitic infection was known to have existed for at least 10 and probably for 14 years. Physical ex-

TABLE II

Results of Titered Serologic Tests for Syphilis Performed on Fresh and on Preserved Sera in Case 2
Late cardiovascular syphilis with aortic regurgitation and late asymptomatic neurosyphilis*

Days	Provocative Agent	Kahn		Cardiolipin	
		Fresh Sera	Frozen Sera	Fresh Sera	Frozen Sera
−17		1–40		1–32	
−10		1–40		1–16	
−2		1–30	1–40	1–8	1–16
0	Pro. Pen. 600,000 U.	1–30	1–40	1–32	1–16
3		1–40	1–40	1–32	1–16
4	Pro. Pen. 600,000 U.	1–20	1–40	1–16	1–16
6		1–50	1–30	1–16	1–16
7	Pro. Pen. 600,000 U.				
11	Pro. Pen. 600,000 U.				
14	Pro. Pen. 600,000 U.	1–60	1–40	1–16	1–16
18	Pro. Pen. 600,000 U.	1–30		1–32	
21	Pro. Pen. 600,000 U.				
25	Pro. Pen. 600,000 U.	1–40	1–40	1–32	1–16
Range of Variation		1–20 to 1–60	1–30 to 1–40	1–8 to 1–32	1–16
Dilution Difference		4	1	2	0

* See footnote, table 1.

amination revealed no clinical evidence of the disease. The STS * was reported as Kahn positive in a 1:30 dilution, cardiolipin positive, 1:8. The cerebrospinal fluid contained 847/3 cells, total protein = 163 mg. per cent, complement-fixation test positive in from 1.0 c.c. to 0.03 c.c. of spinal fluid, colloidal test = 5543320000. The final diagnosis was late asymptomatic neurosyphilis.

After three quantitative blood tests for baseline observation, Mapharsen was injected in a dosage 0.06 gm.; subsequently on the seventh, fourteenth and twenty-eighth days, bismuth subsalicylate, 0.2 gm., was administered intramuscularly. In fresh sera there was great variation, the Kahn titers ranging from positive undiluted to positive 1:30, and the cardiolipin from positive undiluted to 1:16. With frozen sera, the range of variation was less: Kahn positive from 1:10 to 1:30, cardiolipin

* STS = serologic test for syphilis.

from positive 1:2 to doubtful in undiluted serum. There was no suggestion of a provocative effect in the serologic pattern.

Case 4. This 34 year old Negro woman had syphilis of long but unknown duration. On physical examination the only abnormality was related to the pupils, which were contracted and which did not react to light. Evidence of posterior column disease was absent. The initial Kahn titer was positive 1:5, cardiolipin positive 1:8. The cerebrospinal fluid contained 378/3 cells, total protein = 121 mg. per cent, complement-fixation test positive in from 1.0 c.c. to 0.12 c.c. of spinal fluid, colloidal test = 5554310000. The diagnosis was late unclassified (so-called diffuse meningovascular) neurosyphilis.

After obtaining three blood tests, Mapharsen 0.06 gm. was administered and further blood tests were obtained on the second, fourth and seventh days thereafter. Subsequently, a water-soluble bismuth compound was injected weekly for four weeks, serum for titration being obtained before each injection. With fresh sera, the range

TABLE III

Results of Titered Serologic Tests for Syphilis Performed on Fresh and on Preserved Sera in Case 4
Late meningovascular neurosyphilis*

Days	Provocative Agent	Kahn		Cardiolipin	
		Fresh Sera	Frozen Sera	Fresh Sera	Frozen Sera
−18		1–5		1–8	
−7		1–5		1–4	
0	Maph. 0.06 gm.	1–10	1–5		1–4
2		1–5	1–5	1–4	1–4
4		1–5	1–5	1–4	1–2
7	Thiobismol 0.2 gm.	1–5	1–5	1–2	1–4
14	Thiobismol 0.2 gm.	Undil.	Undil.	Undil.	1–4
21	Thiobismol 0.2 gm.	1–10	Undil.	1–4	1–2
28	Thiobismol 0.2 gm.	1–20	Undil.	1–4	1–2
Range of Variation		Undil. to 1–20	Undil. to 1–5	Undil. to 1–8	1–2 to 1–4
Dilution Difference		3	1	3	1

* See footnote, table 1.

of variation with the Kahn technic was from positive undiluted to positive 1:20, with cardiolipin from positive in undiluted serum to positive 1:8. With sera preserved by freezing, the Kahn varied from positive undiluted to positive 1:5, the cardiolipin from positive 1:2 to 1:4. As indicated in table 3, there was no provocative serologic effect. However, if Thiobismol alone had been used, and if serologic testing had been limited to the fourteenth, twenty-first and twenty-eighth days, the rise in Kahn titer in fresh serum from positive, undiluted to positive in a 1:10 dilution, and finally in a 1:20 dilution, might have been interpreted as evidence of a provocative effect. The cardiolipin titer likewise "rose" from positive undiluted to positive in a 1:4 dilution, but the titers on preserved sera tested simultaneously remained either unchanged (Kahn) or showed a "fall" from positive in a 1:4 dilution to a 1:2 dilution (cardiolipin). These results are within the range of laboratory variations in sensitivity of the tests and are not due to changes in the patient's serum.

Case 5. This 44 year old Negro man had clinically latent syphilis of uncertain duration but probably late, in view of his age. The initial STS was reported as Kahn

positive 1:110, cardiolipin positive 1:64. The cerebrospinal fluid contained 173/3 cells, and the quantitative complement-fixation test was positive in from 1.0 c.c. to 0.12 c.c. The diagnosis was asymptomatic neurosyphilis.

The provocative agents employed were Mapharsen in a dosage of 0.08 gm., followed one week later by bismuth subsalicylate, 0.2 gm., and by two subsequent injections of the same material at weekly intervals. The results of the Kahn tests showed great variation ranging from positive 1:60 to positive 1:180 in fresh sera, and from 1:40 to 1:130 in frozen sera. The results of the cardiolipin test showed less variation—fresh sera positive 1:8 to 1:128, frozen sera positive 1:8 to 1:32 (table 4).

From the standpoint of a provocative serologic effect, if only selected portions of table 4 were available, rather than all the results recorded, evidence for a provocative effect could be adduced. For example, the cardiolipin test on fresh serum

TABLE IV

Results of Titered Serologic Tests for Syphilis Performed on Fresh and on Preserved Sera in Case 5
Late asymptomatic neurosyphilis*

Days	Provocative Agent	Kahn		Cardiolipin	
		Fresh Sera	Frozen Sera	Fresh Sera	Frozen Sera
−14		1–110		1–64	
−3		1–60	1–130	1–16	1–32
0	Maph. 0.08 gm.	1–180	1–140		1–32
1		1–120	1–40	1–128	1–32
3			1–120		1–116
5		1–110		1–128	1–8
7	Bi. Sub. 0.2 gm.	1–100	1–110	1–32	1–8
14	Bi. Sub. 0.2 gm.	1–100	1–80	1–32	1–8
21	Bi. Sub. 0.2 gm.	1–80	1–60	1–8	1–8
Range of Variation		1–60 to 1–180	1–40 to 1–130	1–8 to 1–128	1–8 to 1–32
Dilution Difference		12	8	4	2

* See footnote, table 1.

three days before the injection of Mapharsen was positive in a dilution of 1:16. On the first and fifth post-treatment days the titer "rose" to positive 1:128 and subsequently "fell" to 1:32 and finally to 1:8. A similar trend is suggested by the results of the Kahn test on fresh sera, but the highest titer (1:180) was reported on serum drawn before rather than after the injection of the provocative agent. The results of both tests performed on sera preserved by freezing give no indication of a provocative change. The range of variation in this instance was unusually great.

Case 6. This patient was a 27 year old white woman who was discovered to have syphilis when her seven year old daughter developed interstitial keratitis due to congenital syphilis. No evidence of syphilitic infection was present on examination of the mother. The initial STS was reported as Kahn positive in undiluted serum only, and the result of the cardiolipin test was similar. The cerebrospinal fluid was normal. The diagnosis, therefore, was late latent syphilis with duration of infection of at least seven years.

Serum was obtained for serologic testing at the usual intervals, while Mapharsen (0.06) and bismuth subsalicylate were the provocative agents used. The serum

titers with both fresh and preserved sera showed but slight variation over the entire period, and no provocative effect was observed.

Case 7. This patient, a 44 year old Negro woman, had syphilis of unknown but probably long duration, in view of her age, and presented no clinical evidence of the disease. The initial STS was positive by the Kahn technic in a dilution of 1:30, and 1:16 with cardiolipin. The cerebrospinal fluid was abnormal, with an elevated total protein (74 mg. per cent), a positive complement-fixation test and a first zone colloidal test. The diagnosis was late asymptomatic neurosyphilis.

Serum for titration was obtained at frequent intervals, while Mapharsen (0.05 gm.) and Thiobismol (0.2 gm.) were employed successively as provocative agents, the latter in three doses at weekly intervals. Quantitative Kahn and cardiolipin tests varied in positivity from 1:30 to 1:70 and 1:8 to 1:32, respectively, on fresh sera, and from 1:40 to 1:60 and 1:16 to 1:32 on preserved sera. There was no provocative effect.

Case 8. This patient, a 32 year old Negro woman, had syphilis of unknown duration, with abnormal pupils and evidence of posterior column degeneration. Serologic tests for syphilis were of low titer, the Kahn and cardiolipin both being initially reported as doubtful on fresh serum. The cerebrospinal fluid was abnormal, with 92/3 cells and a positive complement-fixation test. The diagnosis was tabetic neurosyphilis.

The initial provocative agent used was Mapharsen (0.08 gm.), followed by bismuth subsalicylate at weekly intervals for three weeks. Meanwhile, serum was obtained for serologic testing at the usual intervals. There was no indication of a provocative effect.

Case 9. This 36 year old Negro man had syphilis of 18 years' duration, with a gumma of the nasal septum. The admission titer was positive 1:40 (Kahn) and 1:4 (cardiolipin), and the cerebrospinal fluid was normal. The diagnosis was late osseous and mucosal syphilis.

Mapharsen (0.07 gm.) and Thiobismol were the antisyphilitic agents used, and serum for serologic testing was obtained at appropriate intervals. No provocative serologic effect was evident.

Case 10. This patient was a 43 year old Negro woman with syphilitic infection of 25 years' duration and without clinical evidence of disease. Serologic tests for syphilis were positive in low titer—Kahn 1:5 dilution, cardiolipin in undiluted serum only. The cerebrospinal fluid was abnormal, with 13/3 cells, total protein = 53 mg. per cent, and complement-fixation test positive in from 1.0 c.c. to 0.12 c.c. of spinal fluid. The diagnosis was late asymptomatic neurosyphilis.

Mapharsen (0.08 gm.) was the first antisyphilitic agent employed, followed at weekly intervals by two injections of Thiobismol, and finally by one injection of procaine penicillin in oil. No serologic effect was evident, the results of all tests remaining within the range of laboratory variation.

Case 11. This patient, a 41 year old Negro man, had syphilis of unknown but probably long duration. The admission STS was reported as Kahn positive in a 1:30 dilution, cardiolipin positive in 1:16. The cerebrospinal fluid contained 214/3 cells, total protein = 60 mg. per cent, complement-fixation test positive in from 1.0 c.c. to 0.06 c.c. of spinal fluid, colloidal test = 5543321000. The diagnosis was late asymptomatic neurosyphilis.

Serum for titration was obtained at frequent intervals, while procaine penicillin in oil (600,000 units) was administered twice weekly for three weeks. The Kahn results on fresh serum showed great variation, ranging from positive in a 1:30 dilution to 1:100. Other tests showed no more than a two dilution difference and the cardiolipin test on preserved sera remained constant. A "rise" in Kahn titer on fresh sera followed the initial injection (1:60, 1:80, 1:100), and might have been

interpreted erroneously as a provocative effect, but cardiolipin tests run in parallel showed no such change.

Case 12. This patient was a 45 year old Negro woman with syphilis of unknown duration and without clinical evidence of disease. The initial serologic tests were positive, Kahn 1:50, cardiolipin 1:2. The cerebrospinal fluid contained 39/3 cells and the complement-fixation test was positive in 1.0 c.c. and 0.5 c.c. spinal fluid. The diagnosis was late asymptomatic neurosyphilis.

Procaine penicillin in oil was administered twice weekly in a dosage of 600,000 units for four weeks. Frequently repeated quantitative tests showed considerable variability but no trend indicative of a provocative effect.

Summary of Results

This study represents an attempt to demonstrate a rise in circulating syphilitic reagin by standard quantitative technics following the injection of antitreponemal agents into 12 patients with late syphilis. The clinical material included eight patients with asymptomatic neurosyphilis (one of whom also had syphilitic aortic regurgitation), and one each of benign late (gummatous) syphilis, tabetic neurosyphilis, meningovascular neurosyphilis and late latent syphilis. All patients with neurosyphilis had "active" (Dattner-Thomas) [20, 21] spinal fluids in terms of increased cell counts, elevated total proteins, or both. No evidence of a provocative serologic effect was observed either immediately, i.e., within the first week of injections of Mapharsen or of procaine penicillin, or delayed following subsequent injections of bismuth or of penicillin over a three to four week time period.

Although in three patients an apparent rise in titer occurred at some time during the course of serologic testing when the test was performed with one technic on fresh serum, a similar rise was not evident in the results of the other technic performed on the same serum, nor with either technic when the serum was preserved by freezing and all specimens tested simultaneously. These serologic variations, therefore, were due not to changes in the patients' serum but to day-to-day variations in laboratory sensitivity.

Discussion

In the present attempt to demonstrate a provocative rise in serologic titer, the selection of patients for inclusion in the study requires comment. The first requirement was proof of syphilitic infection. It was therefore necessary to eliminate patients with latent syphilis, since convincing proof of infection is usually difficult to establish. There was one exception, the mother of a child who had stigmata of congenital syphilis. The requirement of proof of infection explains the high proportion of patients with neurosyphilis.

Duration of syphilitic infection was a second consideration. It is well known that a rise in serologic titer may follow the institution of antisyphilitic treatment in patients with primary syphilis. Although this has been interpreted by some observers as a provocative effect of the treatment adminis-

tered, a more reasonable explanation is that the rise in titer represents a delay in arrest of the mechanism of reagin formation. However, this type of patient presents no difficulty in diagnosis; the problem under consideration arises most frequently in patients without historical or clinical evidence of syphilis and who, if infected, presumably have had the disease for several or more years. Consequently, patients were selected who either on the basis of history had syphilis of long duration, or who, in the absence of a history of early manifestations, probably had late syphilis because of age.

Since previously administered treatment for syphilis might modify or suppress a provocative serologic effect, only untreated patients have been included.

From the standpoint of serologic status, the sera of half of the patients were in the low-titered range; the remainder had moderately elevated or high-titered tests. It is the former circumstance in which the diagnosis of syphilis is more often in doubt, but by a priori reasoning a provocative rise might be more readily demonstrable in patients whose mechanism of reagin formation was well established; and it was for this reason that patients of this type were included.

The quantitative serologic tests for syphilis employed were those routinely performed in our laboratory, and the standard dilution technics were used. The same or similar tests and methods of quantitation are widely available to physicians in this country and would therefore generally be employed, whereas intermediate dilutions and similar refinements in technic are experimental rather than practical procedures.

The results of this study indicate that a rise in quantitative titer following the injection of antitreponemal agents into patients with late syphilis occurs either infrequently (less than once in 12 patients), or in such minute increments of circulating reagin as not to be detected by standard quantitative technics. In either event, it is apparent that provocative testing is of no practical value to the physician for the differentiation of patients with syphilis from those with biologic false positive reactions.

The variation in sensitivity of quantitative serologic tests for syphilis due to technical factors in the laboratory is strikingly demonstrated in several of the patients studied. This was more evident in high-titered than in low-titered sera, and with the Kahn as compared with the cardiolipin technic. Our results amply confirm those of Mohr and Smith [16] in emphasizing the importance of utilizing preserved sera and simultaneous serologic testing when studying trends in titer of syphilitic reagin. By this method, technical variations are minimized but not entirely abolished. The superiority of this procedure is demonstrated by a comparison of the dilution differences. Using fresh sera submitted to the laboratory on the day of bleeding, the range of variation as indicated by the median dilution difference of the 12 patients was three with the Kahn technic, two with cardiolipin. On sera preserved and titered simultaneously, the median dilution difference was 2

with the Kahn test, 1 with cardiolipin. In previous studies of the provocative serologic reaction, day-to-day variations in laboratory sensitivity have not been controlled by the use of preserved sera.

Summary

1. The provocative serologic reaction has been studied in 12 patients with untreated late syphilis.

2. Using standard quantitative technics, Kahn and cardiolipin serologic tests for syphilis were performed before and at frequent intervals after the injection of three antitreponemal agents (Mapharsen, bismuth, procaine penicillin).

3. Titration was performed on fresh sera as obtained from day to day and, in order to minimize variations in laboratory sensitivity, on the same sera preserved by freezing and tested simultaneously.

4. Under the conditions of these experiments, no evidence of a provocative serologic effect was observed.

5. The results reported reëmphasize the importance of day-to-day variations in laboratory sensitivity of serologic tests for syphilis, and the necessity of using preserved sera tested simultaneously for studying serologic trends.

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CORTISONE AND GOLD THERAPY IN CHRONIC RHEUMATOID ARTHRITIS *

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This study of cortisone and gold therapy in rheumatoid arthritis appeared to be of interest since cortisone, despite its remarkable effect in this disease,[1] has not proved of expected value. It was hoped that this steroid would permanently and completely inactivate rheumatoid arthritis. However, there is evidence [2, 3, 4] that in most instances cortisone acts only as a suppressive agent, and it is known that undesirable physiologic actions may result from its prolonged administration.[5] Hence, it appeared worth while to determine if cortisone and gold given concurrently, or if cortisone given to patients already receiving gold, would increase the effect of gold or cortisone so that the disease process of rheumatoid arthritis would be more rapidly and permanently inactivated, than if cortisone or gold were administered alone.

For this purpose, 92 patients with active chronic rheumatoid arthritis with various stages of involvement, who had been under observation for adequate intervals, were divided into four series, as follows: First, eight patients who were receiving gold with only moderate benefit were given cortisone in addition to the gold; second, 13 patients were given gold and cortisone concurrently; third, 42 patients were given gold alone; and fourth, 29 patients were given cortisone alone. For comparison, 273 patients who received neither gold nor cortisone were also restudied.[6]

Patients in study were classified according to the Therapeutic Criteria of the American Rheumatism Association.[7] This was also followed in the analysis of the results.

Laboratory

Laboratory examination in this study included complete blood counts, eosinophil counts, sedimentation rates, urinalysis and blood chemistry determinations, including sodium, potassium, cholesterol and sugar. These will be reported at a later date.

Dosage Levels of Cortisone and Gold

The dosage levels of cortisone and gold, unless altered for experimental or other purposes, were as follows: Cortisone: 100 mg. intramuscularly every eight hours for 24 hours, then every 12 hours for 24 hours; and then

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100 mg. daily for 21 days. Cortisone was then discontinued until a relapse occurred. It was then reinstituted at the previous level and, after 14 days, 75 to 100 mg. were given every other day parenterally, or 50 to 75 mg. per day orally. Cortisone was then again discontinued at various intervals. Chrysotherapy: 10 mg., first given either intramuscularly or intravenously, and followed at weekly intervals by 50 mg. until a total 1.0 gm. had been given. Gold was then continued at 10, 14, 21 and 30 day intervals. The amount of gold given represents the metal content of the agent.*

Observations

The observations in this study, noted in tables 1, 2, 3 and 4 were: duration of the arthritis; classes of functional impairment and structural change on admission; total days and amounts of cortisone and gold given; present status of the patients in regard to gold and cortisone; change in functional impairment; therapeutic response, and length of remission. Some of these studies were also made for comparison on the series of patients previously reported who received neither gold nor cortisone.

The results in these different series are unlike and will first be considered separately, then summarized.

Patients Receiving Gold When Cortisone Was Added

The data on the first series of eight patients (who were receiving gold when cortisone was added) are shown in table 1. They are as follows: The duration of the arthritis was two, 10, 22, nine and one-half, 10, three, four and 30 years; the functional impairment was Class III in five and Class IV in three patients; the structural change was Class II in three, Class III in two and Class IV in three patients; the total amounts of cortisone given were 22.625, 20.54, 18.40, 9.00, 7.85, 14.05, 14.65 and 20.5 gm. over periods of 391, 406, 404, 200, 129, 290, 262 and 365 days, respectively; the total amounts of gold given prior to and during cortisone therapy were 2.771, 2.69, 2.667, 2.75, 0.75, 4.063, 2.067 and 3.0 gm. for periods of 554, 784, 1173, 600, 274, 1641, 474 and 1,095 days; the change in functional impairment (five Class III, three Class IV) was one to Class I, six to Class II, and one to Class III. The therapeutic response to gold was seven Grade II, one Grade III, and to cortisone and gold, eight were Grade II; remission, after cortisone was discontinued, lasted 33, 24, 10, 10, 42, 0, 39 and 21 days. None of the remissions was complete. All eight patients relapsed and are now receiving both gold and cortisone.

Remissions were of shorter duration in two patients after the second withdrawal of the cortisone. One patient (case 5), whose first remission (incomplete) lasted 42 days, experienced a similar remission of only 22 days the next time cortisone was discontinued. The other patient (case 7)

* Aurol Sulfide, Myochrysine, Solganal B Oleosum, Gold Sodium Thiosulfate.

TABLE I

Eight patients with chronic rheumatoid arthritis receiving gold when cortisone was added. The duration of the arthritis, the classes of functional impairment and structural change, the total days and amounts of both cortisone and gold, the present status in regard to the drugs, the change in functional impairment and the therapeutic response are listed.

Patients	1*	2	3*	4*	5*	6	7*	8*
1. Arthritis Duration—Years	2	10	22	9.5	10	3	4	30
2. Functional Impairment—Class	IV	III	IV	III	III	III	III	IV
3. Structural Change—Class	II	IV	IV	II	III	II	III	IV
4. Totals—Cortisone								
Days	391	406	404	200	129	290	262	365
Grams	22.625	20.54	18.40	9.00	7.85	14.05	14.65	20.5
Gold								
Days†	554	784	1173	600	274	1641	474	1095
Grams†	2.771	2.69	2.667	2.75	0.75	4.063	2.067	3.0
5. Functional Impairment (Change) Class	IV-III	III-II	IV-II	III-II	III-II	III-I	III-II	IV-III
6. Therapeutic Response								
Gold Grades	3	2	2	2	2	2	2	2
Cortisone Grades	2	2	2	2	2	2	2	2
7. Remission after Cortisone—Days								
First	33	24	10	10	42	0	39	21
Next					22		10	21

* Gold previously with Grade I response.
† Metal content. Present status—All receiving gold and cortisone.

had an incomplete remission of 39 days after the first withdrawal and of only 10 days after the next discontinuance of the hormone.

It is seen that the patients who were receiving gold with moderate benefit when cortisone was added had exhibited a good therapeutic response and increased functional capacity following gold. The addition of cortisone to this therapy again produced a good therapeutic response which persisted only as long as cortisone was administered, or for short periods of from 0 to 42 days thereafter. A complete remission occurred in none of the patients, and there was no uniform increase in the functional capacity. It is apparent in this group that cortisone did not increase the effect of the gold.

PATIENTS GIVEN GOLD AND CORTISONE CONCURRENTLY

Observations in the series of 13 patients (table 2) who were given cortisone and gold concurrently may be summarized as follows: Reactions to gold had occurred in seven of the patients who had received it previous to this study. In six of the seven, the reaction was so severe that gold was discontinued. Three patients (cases 1, 2 and 5) were 10, six and five years of age, while 10 were adults. The duration of the arthritis was three, five, one and one-half, four, nine, 10, 12, eight, 10 and four years, and seven, two and five months. The functional impairment was two Class II, eight Class III, and three Class IV. The structural change was one Class I; nine Class II, and three Class III. The total amounts of cortisone given were 3.475, 4.46, 3.8, 7.0, 5.975, 5.85, 14.55, 1.35, 3.0, 5.79, 22.94, 9.9 and 2.450 gm.

TABLE II

Summary of 13 patients with chronic rheumatoid arthritis who received gold and cortisone concurrently, showing the duration of the arthritis, the classes of functional impairment and the structural change, the total days and amounts of cortisone and gold given, the change in functional impairment, therapeutic response, the days of remission and the present therapy.

Patients	1*	2*	3	4*	5	6	7	8*	9	10	11*	12*	13*
1. Arthritic Duration	3 yrs.	7 mos.	5 yrs.	1½ yrs.	4 yrs.	2 mos.	9 yrs.	5 mos.	10 yrs.	12 yrs.	8 yrs.	10 yrs.	4 yrs.
2. Functional Impairment (Class)	III	IV	III	III	IV	IV	III	III	III	III	II	II	II
3. Structural Change (Class)	II	III	II	II	II	II	III	II	II	II	II	III	I
4. Totals of Cortisone													
Days	116	122	56	275	106	95	209	19	37	119	359	187	44
Grams	3.475	4.46	3.8	7.0	5.975	5.85	14.550	1.350	3.0	5.79	22.94	9.9	2.450
Totals of Gold													
Days	403	214	118	112	168	163	219	7 R	37	131	108	187	40
Grams†	0.765	0.57	0.867	1.155	0.394	0.778	1.516	0.067	0.267	0.873	0.970	0.675	0.550
5. Functional Impairment	III	IV	III	III	IV	IV	III	III	III	III	II	II	II
Change	I	II	II	II	II	I	II	II	II	II	II	I	I
Classes													
6. Therapeutic Response to Gold and Cortisone													
Grade	1	1	2	2	1	2	2	2	2	2	2	1	1
7. Remission after Cortisone—													
Days													
Initial	5	5	27	7	33	3	0	7	0	5	7	3	0
Next	229	88	0	7	30	0	0	0	0	12	7	0	0
Maximum—Continued	229	88	0	7	30	163	0	0	0	0	0	0	0
Present Therapy	g-C	g	g-C	C	g-C	g	g-C	C	g-C	g-C	g-C	g-C	g-C

g = Gold. C = Cortisone. * Prior gold with reaction. † Metallic gold content. R = Reaction to gold while on cortisone.

for periods of 116, 122, 56, 275, 106, 95, 209, 19, 37, 119, 359, 187 and 44 days. The total amounts of gold given were 0.765, 0.57, 0.867, 1.155, 0.394, 0.778, 1.516, 0.067, 0.267, 0.873, 0.970, 0.675 and 0.55 gm. for periods of 403, 214, 118, 112, 168, 163, 219, seven, 37, 131, 108, 187 and 40 days. The change in functional impairment was as follows: four to Class I, and nine to Class II from three Class II, seven Class III, and three Class IV. The therapeutic response to gold and cortisone was five Grade I, and eight Grade II. Remissions were for five, five, 27, seven, 33, three, 0, seven, 0, five, seven and three days, with one undetermined after cortisone was first discontinued.

Significant remissions followed initial short remissions in three patients after the second discontinuance of cortisone. One patient (case 1), whose first remission lasted only five days after discontinuance of cortisone, had a complete remission lasting 229 days when cortisone was again discontinued. She again relapsed and is now receiving both gold and cortisone. Another patient (case 2) experienced an early remission of five days when cortisone was stopped; later, a complete remission of 88 days followed the withdrawal of the hormone. This remission is still present. The third patient (case 6) had a remission of three days when cortisone was first discontinued, but when cortisone was stopped again a remission of 163 days followed. This patient's remission is still present. This remission is classed as incomplete because of an elevated sedimentation rate with no other signs or symptoms of arthritis.

One reaction to gold (dermatitis, severe) occurred in one of the seven patients who had had previous gold reactions. The other six tolerated the gold well. There appeared to be no evidence that cortisone was masking gold toxicity.

The Functional Change in Response to Therapy With Gold or Cortisone Given Alone or Combined

The American Rheumatism Association Therapeutic Criteria was employed here in the determination of the functional capacity of these patients; i.e., functional impairment is classified from Class I—complete functional capacity with the ability to carry on all usual duties without handicap—to Class IV, which indicates complete loss of functional capacity, those bedridden or unable to care for themselves.

The changes in the functional impairment in 92 patients in response to therapy are shown in table 3. The functional impairment and change were as follows: Eight of these patients given gold, then gold and cortisone, were initially five Class III, and three Class IV; with gold, the functional capacity was increased so that seven were Class II, and one was Class III. When cortisone was added, one was Class I, five were Class II, and two were Class III. Thirteen patients who received gold and cortisone concurrently were initially three Class II, seven Class III, and three Class IV.

With gold and cortisone given concurrently, four became Class I, and nine Class II. Forty-two patients who received chrysotherapy were initially 16 Class II, 21 Class III, and five Class IV. Twenty-one of these became Class I, 15 Class II, five Class III, and one Class IV. Twenty-nine patients who received cortisone alone were initially eight Class II, 12 Class III, and nine Class IV. With cortisone, the functional impairment became seven Class I, 15 Class II, four Class III, and three Class IV.

Thus it is seen that the eight patients who were receiving gold when cortisone was added had already exhibited an increase in functional capacity due to the gold. The addition of cortisone increased the functional capacity

TABLE III

Showing the functional impairment and change with therapy in patients with active chronic rheumatoid arthritis: (8) receiving gold first, then gold and cortisone; (13) gold and cortisone concurrently; (42) gold alone; and (29) cortisone alone.

Patients Receiving	No.	Functional Impairment*		
		Admission	Gold Alone	Gold and Cortisone
†Gold Alone, then Gold and Cortisone	8	5–III 3–IV	→ 5–II → 2–II, 1–III	1–I 5–II 2–III
Gold and Cortisone Concurrently	13	3–II 7–III 3–IV	→	2–I, 1–II 1–I, 6–II 1–I, 2–II
Gold Alone	42	16–II 21–III 5–IV	21–I 15–II 5–III 1–IV	
		Before Cortisone	With Cortisone	
Cortisone Alone		8–II 12–III 9–IV	7–I 15–II 4–III 3–IV	

* A.R.A. therapeutic criteria.

† Patients only moderately improved on chrysotherapy when cortisone was added.

in one patient, and in one the functional capacity was decreased. One of the eight patients resumed full functional capacity. Therefore, the addition of cortisone to chrysotherapy appeared to produce no uniform increase in functional capacity.

In the group who received gold and cortisone concurrently, it is seen that the functional capacity was increased in all but one patient. Four patients returned to full functional capacity, one of these four receiving only gold at this time, the other three both gold and cortisone.

In the 42 patients who were given gold alone there was an increase in functional capacity; 21 of these patients returned to full functional capacity, and this has been maintained by gold.

In the 29 patients who received cortisone alone, an increase in functional capacity occurred in 26. Six of the 29 patients returned to full functional

capacity still receiving cortisone, while one maintains full function without cortisone.

These observations regarding the functional capacity indicate that cortisone will produce, in most instances, an immediate increase. This usually persists only as long as the cortisone is given, or for short intervals thereafter. When cortisone was added to chrysotherapy in patients already benefited by the gold, there was noted no real increase in functional capacity greater than that from the gold alone, although these patients were more comfortable. This effect again lasted only during the administration or for short intervals after the cortisone was discontinued. However, when cortisone was given concurrently with gold, the functional capacity remained increased after cortisone was discontinued in some patients for prolonged periods (i.e., 229, 88 and 163 days). Gold given alone also produced an increase in the functional capacity in nearly all patients.

It must be noted here that the response to gold is a slow process and cannot be compared to the more rapid action of cortisone; but since some increase in functional capacity may be obtained in patients with rheumatoid arthritis by any type of therapy, an increase in functional capacity is not necessarily an indication of a control of the arthritic activity.

The Therapeutic Response to Gold and Cortisone Given Alone or Combined

The therapeutic response to the agents investigated is evaluated according to the Therapeutic Criteria of the American Rheumatism Association. It is classed as follows: Grade I, or complete remission; Grade II, or major improvement; Grade III, minor improvement; and Grade IV, no improvement, or progression of the disease. The last two grades (III and IV) are not considered significant in the evaluation of therapy and are not included in this analysis.

It appeared worth while first to tabulate the significant therapeutic response, i.e., the combination of complete remission and major improvement; and then, to determine which agent or combination would be more likely to arrest the disease, and list in order the most effective drug or combination to produce (A) a complete remission, and (B) complete remission plus major improvement. The results appear in table 4 and may be summarized as follows: In eight patients given gold, then cortisone and gold, none exhibited a Grade I response; eight had a Grade II response. In 13 patients given gold and cortisone concurrently, the response was five Grade I, and eight Grade II. In 29 patients given cortisone alone, the therapeutic response was six Grade I, and 14 Grade II. In 42 patients given gold alone, 17 were Grade I, and six were Grade II; while of 273 patients who received neither gold nor cortisone, 12 were Grade I, and 104 were Grade II.

Complete remissions occurred more frequently in patients who received gold alone, 40.5 per cent (17 out of 42 studied); followed by gold and

cortisone given concurrently, 38.5 per cent (five out of 13); cortisone given alone, 20.7 per cent (six out of 29); neither gold nor cortisone, 4.4 per cent (12 out of 273); and cortisone added to gold therapy, 0 per cent (0 out of eight), in that order.

When the combined Grade I and Grade II therapeutic responses are listed (in complete remission and major improvement), cortisone, either given concurrently or added to chrysotherapy, was more effective, with a 100 per cent response (eight out of eight, and 13 out of 13) than cortisone given alone, 69 per cent (20 out of 29), or gold alone, 54.8 per cent (23 out of 42), or therapy without gold or cortisone, 42.5 per cent (116 out of 273). It is significant that, in the series given gold and cortisone concurrently, two of five patients in complete remission have maintained it without cortisone.

TABLE IV

Lists in order of the most effective combination or therapy to produce (A) complete remission (Grade I), and (B) complete remission and major improvement (Grades I and II).

A. Complete Remission (Grade I)				B. Grades I and II Response			
No.	Therapy	No.	Per Cent	No.	Therapy	No.	Per Cent
42	Gold alone	17	40.5	13	Gold and cortisone concurrently	13	100.0
13	Gold and cortisone concurrently	5	38.5	8	Chrysotherapy, cortisone added	8	100.0
29	Cortisone alone	6	20.7	29	Cortisone alone	20	69.0
273	No gold or cortisone	12	4.4	42	Gold alone	23	54.8
8	Chrysotherapy, cortisone added	0	0.0	273	No gold or cortisone	116	42.5

Further, of the six patients in complete remission who received cortisone alone, only one patient remained well without it.

SUMMARY AND CONCLUSIONS

It is pertinent to mention, first, that this study included eight patients who were only partially responsive to gold therapy (those receiving gold when cortisone was added); and second, that of the 13 patients given gold and cortisone concurrently, seven had received gold prior to the investigation. This latter group might not be so responsive to gold, since they had received it previously. While the number of patients is not adequate for statistical analysis, the following remarks appear warranted.

This study indicates that gold given to patients with active chronic rheumatoid arthritis with moderate benefit apparently did not accrue an additional effect to produce an arrest of the disease when cortisone was added. Despite an excellent therapeutic response, no complete remissions

were observed, and all patients returned to their precortisone state shortly after the hormone was discontinued.

Gold given concurrently with cortisone seemed to arrest rheumatoid arthritis in approximately the same percentage of patients as gold given alone, but it appeared superior to cortisone employed alone, and to therapy without gold or cortisone.

The combination of gold and cortisone administered concurrently gave an excellent therapeutic response, an immediate increase in functional capacity, and produced a complete remission of the arthritis in some patients. These effects continued in a sufficient number of patients when cortisone was discontinued to be of therapeutic significance.

In addition, the concurrent administration of gold and cortisone seems to have several therapeutic advantages: First, patients who have previously been intolerant to gold can be given gold with cortisone with less danger of a reaction (to gold). Second, with cortisone it is possible to institute immediate rehabilitative measures which can be carried out before the gold levels are sufficiently high to be effective. Third, cortisone may be discontinued in the patients who respond to gold.

Finally, although no serious reactions to cortisone at the dosage levels employed were encountered, it is necessary to emphasize again the possible dangers of this type of therapy.

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ACUTE SEVERE UPPER GASTROINTESTINAL HEMORRHAGE: A REVIEW OF 195 CASES *

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Acute upper gastrointestinal hemorrhage is a medical emergency, the proper management of which has been the subject of much controversy. For many years it was believed that the patient should be placed at bed-rest, be given nothing by mouth, and receive no intravenous fluid or blood. The starvation régime was to rest the stomach, and the withholding of intravenous fluids was to prevent an increase in the blood pressure with the possibility of blowing out the clot. In some cases, intubation was done in order to aspirate the acid secretions which might digest the clot. After a period of starvation for varying intervals of time, the patient was given a diet consisting of milk and cream, bland foods and alkali powders. Manheim,[1] in 1926, reported a mortality of only 4.2 per cent by using the starvation régime, but Chiesman,[2] in 1932, reported a mortality as high as 25 per cent.

Lenhartz,[3] in 1904, was probably one of the first to advocate early feeding, recommending milk and eggs from the time of the onset of bleeding. Andresen,[4] in 1927, advised a regimen including immediate feedings of gelatin mixtures, but he still withheld any type of intravenous fluids unless the patients were in a state of shock. In 1939, he reported [5] a mortality of 2.3 per cent in cases treated by this method. LaDue [6] treated patients with a similar regimen and, in 1939, reported a mortality of 6.3 per cent.

After Meulengracht,[7] in 1933, announced the use of a liberal puréed diet, including meat, the plan of early feeding became more widely accepted. In 1947, this same author [8] reported a mortality rate of 2.5 per cent in a series of 1,031 patients treated by this régime during the preceding 15 years.

About the same time that Meulengracht advocated conservative treatment with a free feeding program, Finsterer [9] strongly advised immediate gastric resection for these cases, and reported a mortality of 4.3 per cent. He pointed out the greatly increased mortality rate in those patients who were operated upon after 48 hours. Others, including Wangensteen [10] and Heuer,[11] have emphasized the need for operation in those patients who do not stop bleeding within this period of time.

In the early part of the last decade the trend was to give early, frequent

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feedings of milk and cream, or variations of the Meulengracht or Andresen diets. In addition, blood transfusions were used, but the total amount of blood given was small. Chaiken and Tannenbaum,[12] in 1943, stated that after the use of prompt feeding plus small blood transfusions, their mortality rate dropped by one-half, to 3.1 per cent.

In recent years, blood banks have become common in the larger hospitals, and with the more readily available blood its use in the treatment of gastrointestinal hemorrhage has increased markedly. Welch [13] recommended the use of adequate amounts of blood and also advised the use of an inlying Levine tube. His gross mortality, including those who went to operation, was 13 per cent, although his criteria for severe bleeding were more rigid than in most series. Sandusky and Mayo,[14] with a mortality rate of 10.1 per cent, also gave nothing by mouth until the bleeding had stopped and emphasized the use of immediate and continued transfusions, plus early operation if bleeding continued. Lewison [15] agreed to the liberal use of blood transfusions, but in addition promptly instituted an early feeding program. Bowers and Rossett [16] used essentially the same régime and had a mortality rate of 1.3 per cent. Cates,[17] however, reported a mortality rate of 30 per cent in cases of massive bleeding treated in essentially the same manner.

Thus it is seen that there is still a difference of opinion as to whether the patients should initially have a period of starvation, frequent feedings of milk and cream, or a more liberal diet. Most authors now agree that the giving of blood in large amounts is indicated, although Pollard and Wollum [18] state that it should not be given unless there is definite shock or the hemoglobin is below 50 per cent. The question as to the optimal time for surgery has not been settled. Meulengracht [8] believes all patients should be treated conservatively; Heuer [11] believes operation should be done after 48 hours if medical management fails, and Stewart et al.[19] believe that operation should be done immediately on all patients with acute massive hemorrhage.

Method of Study

At the Veterans Administration Hospital, Louisville, Kentucky, during the five year period from April 15, 1946, to April 15, 1951, all patients with upper gastrointestinal bleeding were routinely admitted to the medical service. During the first three years of this study they were seen by a surgical consultant only if it was thought that an operation might be indicated, but in the last two years the patients have been seen by the surgeons routinely within a few hours of admission.

History. An attempt was made to establish the exact diagnosis and etiology of the bleeding in all cases. Additional history concerning the duration of ulcer symptoms, number of previous bleeding episodes, quality of previous treatment, alcohol consumption and previous surgical experiences and also a roentgen-ray examination were obtained.

Physical Examination. Signs of shock were carefully looked for, and also the presence of arteriosclerosis and other coexisting diseases. Determinations of blood pressure and pulse rate were taken at the time of admission and were repeated every one to four hours.

Laboratory. Red blood cell counts and hemoglobin determinations were done immediately, and blood was drawn for typing and cross-matching. The red cell counts and hemoglobin tests were repeated at four, six, eight or 12 hour intervals, as indicated. Bleeding and clotting time, prothrombin time and platelet count determinations were done during the first three years of the study only if a blood dyscrasia was suspected, but during the last two years they were done routinely on all patients. Liver function tests were performed on all cases suspected of having esophageal varices.

Roentgen-ray. It was the policy to withhold roentgen-ray examination of the upper gastrointestinal tract until at least a week after the bleeding had stopped. It was thought that, even with gentle manipulation at the time of fluoroscopy, there was danger of aggravating the bleeding. Whenever a patient was being considered for surgery, roentgen-ray studies were made if they were desired by the surgical consultant. Also, roentgen-ray examinations were done early if esophageal varices were suspected.

Bed-rest. The patients were placed on absolute bed-rest in a flat position or, if in shock, with the foot of the bed elevated. The patients were kept in bed for from seven to 10 days after the bleeding had stopped and then were progressively ambulated.

Diet and Antacid Therapy. The régime was to place the patient immediately on a diet of 3 oz. of a mixture of one-half milk and one-half cream, which was given hourly from 7:00 a.m. to 9:00 p.m., and 1 oz. of a colloidal aluminum hydroxide preparation, which was given every two hours during the night. In the first half of our study, occasionally the milk and cream mixture was given throughout the night and/or the aluminum gel was given at two to four hour intervals on a 24 hour schedule.

This régime gave the patient antacid therapy throughout the 24 hours. In addition to being an effective buffering agent, the milk and cream mixture provided a sufficient nutritional intake for a patient at bed-rest and also promoted a normal fluid and electrolyte balance.

Approximately 10 days after the bleeding had stopped, usually just after the roentgen-ray studies had been made, a progressive, bland, low-residue diet was substituted for the milk and cream régime.

Antisecretory Drugs. In the early part of the study, either atropine or tincture of belladonna, in varying dosages, was given to most patients. For the past two years atropine, gr. 1/150, has been given hypodermically every six hours to all cases.

Sedation. Sedation was used as indicated, and barbiturates were the drug of choice. Early in the study narcotics were used occasionally, but later they were discontinued because of the possibility of their causing

nausea and vomiting, and because, if the patient had a recurrence of bleeding and went into shock, the vital functions would be more seriously depressed because of the previously administered narcotic.

Blood. The early use of blood transfusions was one of the most important phases in our medical management. An attempt was made in all cases to counteract the shock and to raise the red blood cell count to 3.5 million or slightly over by the use of transfusions. It was also the policy to keep two pints of cross-matched blood in reserve at all times until a week after the bleeding had stopped. The count of 3.5 million was arbitrarily set because it was felt that this provided a sufficient amount of blood, with the patient at bed-rest or on limited activity, to avoid anoxia and to maintain vital functions at a reasonably normal level. In addition, it provided a more adequate margin of safety if the patient had a continuation or recurrence of bleeding. A count higher than this was not deemed necessary. There was also the theoretic consideration that, if more blood were given, it might increase the chance of continued or recurrent bleeding.

Surgery. Whenever it was determined that, in spite of multiple blood transfusions, we were having difficulty keeping up with the blood loss, or that after two or three days there was still active bleeding, then the medical management was felt to be failing and operation was considered. Each case was considered individually, and no time limit established as to when medical management should be abandoned and operation performed. The general condition of the patient, the presence of coexisting disease and the amount of blood available for transfusions were additional factors which were considered in making the decision to continue medical management or to advise surgical intervention.

Results of Study

During the five year period from April 15, 1946, to April 15, 1951, there were 363 patients admitted to this hospital with a history of having had gross upper gastrointestinal hemorrhage, or who developed a hemorrhage during their hospitalization.

We have classified these patients into three groups:

Group 1: Those who gave a history of gross bleeding but in whom no objective evidence of bleeding was found after admission.

Group 2: Those who gave a history of bleeding which was substantiated by tarry stools or by hematemesis, but who gave no evidence of being in shock, and whose lowest red blood cell count did not go below 3.5 million.

Group 3: Those who gave a history of or who had symptoms of bleeding and who, in addition, gave evidence of being in shock or whose red blood cell count was below 3.5 million. This last group was felt by us to be in the category of acute severe hemorrhage.

In Group 1, there were 76 patients; in Group 2, 71 patients, and in Group 3, 215 patients.

As stated above, we consider that only in those patients in Group 3 was the bleeding sufficient to be classed as severe. There were 215 admissions in this group, including 14 for esophageal varices, three for sarcoma of the peritoneum with invasion of the stomach, two for carcinoma of the stomach, and one for carcinoma of the pancreas with erosion into the duodenum.

This paper, however, will henceforth be concerned only with the 195 admissions for bleeding from benign ulcer, hiatal hernia (in which there may have been an ulcer), hypertrophic gastritis, and the cases of undetermined etiology. The 20 patients who were bleeding as a result of esophageal varices or neoplastic diseases are being excluded because they were bleeding from pathologic processes which presented a different prognosis and required special types of management, in comparison with those cases in which we desired to evaluate a particular pattern of management. The number of cases in each of these categories which we included in our study is shown in table 1.

TABLE I

Etiology of Severe Upper Gastrointestinal Bleeding

	Number	Percentage
Duodenal ulcer	114	58.6%
Gastric ulcer	19	9.7%
Hypertrophic gastritis	10	5.1%
Marginal ulcer	3	1.5%
Esophageal ulcer	1	0.5%
Hiatal hernia	1	0.5%
Undetermined etiology	47	24.1%
Total	195	100.0%

These 195 admissions represent 179 patients, of whom 12 had two admissions and two had three admissions for bleeding.

Diagnosis. A diagnosis of ulcer was not made in any case without roentgen-ray, surgical or autopsy confirmation. Likewise, a diagnosis of hypertrophic gastritis was made only with positive roentgen-ray, gastroscopic or surgical findings. The group with hemorrhage due to undetermined cause includes many patients who gave a history suggestive of peptic ulcer, and several in whom peptic ulcer had been diagnosed elsewhere in the past but in whom it was not demonstrated by us.

Age. Table 2 shows the age groups of our patients. It is to be noted that 79 cases (40.5 per cent) of the entire group were over the age of 50. Of the patients with duodenal ulcer, 41.2 per cent were over 50 years of age, whereas of the patients with gastric ulcer, 57.9 per cent were over that age.

It is also seen that the preponderance of patients was grouped in the third and fourth decades or in the sixth decade. This may be explained in part by the fact that all of our patients were veterans, and the veteran population as a whole is roughly divided into two age groups, because of World Wars I and II.

Sex. All of our patients were males, which is explained in part by the fact that less than 1 per cent of the admissions to this hospital are females.

Race. There were 179 (91.8 per cent) white patients and 16 (8.2 per cent) colored patients, which corresponds roughly to the proportion of white to colored patients admitted to the hospital.

Occupation. Most of the common occupations were represented, and there was no preponderance of patients engaged in any one.

Season. There was no significant seasonal variation in the number of admissions of the entire group. However, when only the proved ulcer cases are considered, there was a slightly higher number of admissions in the spring and fall.

Past History. Twenty-five patients (12.8 per cent) gave no history of previous symptoms suggestive of peptic ulcer. Fifteen patients (7.7 per cent) gave a history of ulcer symptoms of less than one month's duration. There were 12.8 per cent who had had symptoms for from one month to one year, 35.5 per cent for from one to five years, and 31.3 per cent for over five years, including 4.6 per cent who had had symptoms for over 20 years. A diagnosis of peptic ulcer by roentgen-ray had been made in the past in 58 cases (29.8 per cent).

TABLE II

Incidence of Bleeding According to Age

Etiology	Total	20–29	30–39	40–49	50–59	60–69	Over 70 yrs.
Duodenal ulcer	114	26.3%	18.4%	14.0%	31.6%	6.2%	3.5%
Gastric ulcer	19	15.8%	10.5%	15.8%	41.2%	5.3%	10.5%
Miscellaneous	15	0.0%	33.3%	33.3%	26.7%	6.7%	0.0%
Undetermined	47	29.8%	27.6%	8.5%	25.5%	4.3%	4.3%
Total	195	24.1%	21.0%	14.4%	30.8%	5.6%	4.1%

The majority of these patients had had poor or no treatment for their gastrointestinal symptoms prior to their present bleeding episode. Only 2.6 per cent had received what was considered satisfactory treatment, in that they were on a bland diet, abstained from alcohol and received antacid medication for their acute symptoms. Previous operation for ulcer had been done in 16 (8.2 per cent) of the cases, and in three of these the operation had been done for hemorrhage.

There were 47 cases (24.1 per cent) who had had previous bleeding, 25 patients having had only one previous episode, 10 having had two, three having had three, three having had four and six having had more than four previous episodes. In most cases it was impossible to determine from the history the severity of these previous hemorrhages.

Present Bleeding Episode. We did not consider any patient to have had an acute bleeding episode, nor did we include him in this study, if the bleeding had occurred more than 14 days prior to admission, unless he was

still actively bleeding or had had evidence of shock at the time of admission to the hospital. In attempting to determine the duration of bleeding prior to the present admission, it was estimated that 71 (36.4 per cent) had been bleeding for one day or less; 40 (20.5 per cent) for two days or less; 25 (12.8 per cent) for three days or less; 43 (22.0 per cent) for from four to seven days, and 16 (8.2 per cent) for from seven to 14 days. Thus, 136 (69.8 per cent) of the patients gave a history of having been bleeding for less than 72 hours prior to admission.

The bleeding was manifested by hematemesis in 21 (10.8 per cent), by melena in 65 (33.4 per cent), and by both hematemesis and melena in 109 (55.8 per cent) of the patients. Thus, 66.6 per cent of the patients had hematemesis and 89.2 per cent melena. There was a slightly higher incidence of hematemesis in the cases with gastric ulcers (73.7 per cent), than in those with duodenal ulcers (62.3 per cent).

TABLE III

Incidence of Coexisting Diseases

Disease	Cases	Per Cent	Disease	Cases	Per Cent
Arteriosclerosis	31	15.9%	Asthma	2	1.0%
Cardiovascular disease	26	13.3%	Urinary tract calculi	2	1.0%
Hypertension	13	6.7%	Psychosis	2	1.0%
Alcoholism with delirium	5	2.6%	Hydronephrosis	1	0.5%
Diabetes	4	2.1%	Carcinoma of prostate	1	0.5%
Nephritis	3	1.5%	Bronchogenic carcinoma	1	0.5%
Pulmonary tuberculosis	3	1.5%	Infectious hepatitis	1	0.5%
Pyelitis	3	1.5%	Chronic pancreatitis	1	0.5%
			Biliary cirrhosis	1	0.5%

Pain was associated with the bleeding in 109 cases (55.8 per cent), but there was no increased incidence of pain in any of the different groups. A history of syncope was obtained in 67 (34.4 per cent).

Coexisting Diseases. On admission it was found that one or more coexisting diseases of major significance were present in 58 (29.8 per cent) of the 195 cases. The incidence of coexisting disease was twice as high in those with gastric ulcer as in those with duodenal ulcer.

The incidence of the most commonly associated diseases present was as follows: moderate or severe arteriosclerosis in 31 (15.9 per cent); cardiovascular disease in 26 (13.3 per cent), and hypertension in 13 cases (6.7 per cent). In addition to the above three, there were 30 other associated diseases present in 29 patients. In many cases these other diseases were present in addition to the hypertension, arteriosclerosis or cardiovascular disease. The incidence of these coexisting diseases is shown in table 3.

Physical Findings. Evidence of shock was present in 39 (20 per cent) of the patients. The blood pressure was less than 100 systolic in 51 (26.1 per cent), 101 to 140 in 128 (65.7 per cent), and above 140 in 16 (8.2 per

cent). The pulse was less than 100 in 122 (62.6 per cent) and above 100 in 73 (37.5 per cent).

Laboratory Data. As an indication of the severity of bleeding, we have taken the patients' lowest red blood cell count and hemoglobin determinations. As is indicated in table 4, 187 (95.9 per cent) of the total 195 cases had a red blood cell count of less than 3.50 million. The remaining eight cases were included in our series because, in spite of a red cell count of over 3.5 million, they were in shock at the time of admission. The distribution of cases according to red cell levels is shown in table 4. In all cases the lowest hemoglobin determinations corresponded to the lowest red blood cell determinations.

Bleeding and clotting time, prothrombin time and platelet count determinations were done on more than one-half of the patients. Using the above determinations, plus other physical and laboratory findings, there was no case in which a diagnosis of blood dyscrasia could be made.

TABLE IV

Incidence of Cases According to Lowest Red Cell Count

Red Count	Number	Percentage
1.0–1.5 M	9	4.6%
1.5–2.0	29	14.9%
2.0–2.5	44	22.6%
2.5–3.0	58	29.7%
3.0–3.5	47	24.1%
3.5–4.0	7	3.6%
4.0–4.5	1	.5%
Total	195	100.0%

Roentgen-ray. A roentgenologic examination with contrast medium was made in 178 (91.3 per cent) of all the cases. This examination was performed within three days of admission in eight (4.1 per cent) of the cases; within four to seven days in 22 (11.3 per cent); within eight to 14 days in 86 (44.1 per cent); within 15 to 21 days in 42 (21.5 per cent), and after 21 days in 20 (10.3 per cent). Thus, an early roentgen-ray examination (in seven days or less) was done in only 30 (15.4 per cent) of all cases. In this group of 30 cases in which early roentgenologic studies were done, a positive diagnosis was made in two-thirds.

Gastroscopy. Gastroscopy was done as an interval procedure in seven (3.6 per cent) of the 195 cases. All examinations were done at least two weeks after the bleeding had stopped and after roentgen-ray studies had been made. In five cases it was used because roentgen-ray and other examinations had not given a definite diagnosis. In one of these cases a diagnosis of gastritis with multiple bleeding points was made, and in the other four the examination was negative. Gastroscopy was done once to visualize a supposedly nonhealing gastric ulcer, and once because the roentgenologists were uncertain as to the presence of a gastric ulcer. In both of these cases the examination was negative.

General Treatment. The milk and cream diet with antacid, on a 24 hour basis, was used in all but eight cases. In these latter patients, persistent nausea and vomiting precluded its use. Antisecretory drugs were used in about three-fourths of the patients. Barbiturates were used as sedation in two-thirds of the cases, and narcotics in 12 per cent. No ill effects were encountered from the use of any of the antisecretory drugs, sedatives or narcotics.

Intubation. A Levine tube was used in five cases to relieve distention secondary to pyloric obstruction, and in one case to give milk and cream to a psychotic patient.

Plasma. Plasma was used to combat shock in 14 (7.2 per cent) of the cases, because blood was not immediately available.

Blood Transfusions. Whole blood transfusions were used in 177 patients (90.8 per cent) and they received a total of 786 pints, for an average of 4.4 pints for each patient.

Control of Hemorrhage. Excluding the cases in whom bleeding was stopped by early operation, or those who died while still bleeding, it was estimated clinically that bleeding had stopped by the end of the first 24 hours in the hospital in 61.7 per cent; by the end of 48 hours in 85 per cent; by the end of 72 hours in 90 per cent, and in all but three cases (1.8 per cent) by the end of four days.

Recurrence. In the entire series, 11 cases (5.6 per cent) had a recurrence of bleeding while in the hospital under treatment. In 10 cases this occurred between the third and fifteenth days, and in one case on the thirty-fifth day. There were seven (6.1 per cent) of the duodenal ulcers, three (15.8 per cent) of the gastric ulcers, and one (2.1 per cent) of the cases due to undetermined cause which had a recurrence of bleeding. There was no higher incidence of recurrence in the younger than in the older age groups.

Complications. With the medical treatment as outlined above, the most frequent complication encountered was constipation, in varying degrees of severity. In 36 cases (18.5 per cent), constipation was a major problem and severe enough to require frequent enemas, including oil retention enemas. Nine of these cases had fecal impactions which required manual removal. Two of the nine developed obstruction with secondary perforation of the bowel, and one ultimately died from this complication. In addition to constipation, there were 19 other complications in 19 cases which were thought to be secondary and directly attributable to the peptic ulcer or associated with the acute bleeding episode. These same 19 patients had seven other complications which were secondary to preëxisting disease. The incidence of complications is shown in table 5.

Only one patient, to our knowledge, developed homologous serum jaundice. This patient had received both plasma and blood, and returned to the hospital three months after his acute bleeding episode with acute hepatocellular jaundice.

Surgery. In the 195 cases there were 23 cases (11.8 per cent) who underwent an early or emergency surgical procedure. Of these, 13 (56.6 per cent) were operated upon because of continuing uncontrolled bleeding; four (17.4 per cent) because of recurrent bleeding, and one (4.4 per cent) because of perforation. Of the remaining five (21.8 per cent), three were operated upon because there was a shortage of compatible blood and it was not considered advisable to continue medical treatment. The other two patients were operated upon because they were in good condition and this admission represented their fourth or fifth bleeding episode, so it was decided not to wait to do interval operation. None of these five cases would have gone to operation early, considering their good response to medical treatment, if there had been sufficient blood available or if they had not had so many previous episodes of bleeding.

As noted above, in the 23 cases undergoing early or emergency surgery, 13 were for uncontrolled bleeding. Of these 13, three (23.1 per cent) were operated upon within the first 24 hours, seven (53.9 per cent) within the

TABLE V

Incidence of Complications in Cases Treated Medically

Secondary to Primary Disease		Secondary to Coexisting Disease	
Constipation, severe	36	Acute pulmonary edema	2
Pyloric obstruction	5	Pyelonephritis	2
Unexplained fever	5	Acute urinary retention	1
Pneumonia	3	Congestive heart failure	1
Perforation of colon secondary to fecal impaction	2	Cerebral thrombosis	1
Psychosis	2		
Paralytic ileus	1		
Lower nephron syndrome secondary to incompatible blood	1		

first 48 hours, 12 (92.3 per cent) within the first 72 hours, and all 13 within four days of admission. The four patients who had operation because of a recurrence of bleeding while in the hospital were operated upon within a few hours of the onset of the recurrence, on the third, seventh, fourteenth and seventeenth days, respectively, after admission.

At operation 16 cases (69.6 per cent) were found to have evidence of active bleeding, 15 of these being arterial bleeding in gastric or duodenal ulcers, and one being from multiple bleeding points in a hypertrophic gastritis. In four cases (17.5 per cent) a duodenal ulcer was found but there was no active bleeding, and in three cases (13.1 per cent) there was no evidence of any disease process. In one of these three cases only palpation of the duodenum and not a duodenostomy was done at the time of operation, and 17 days later a duodenal ulcer was demonstrated on roentgen-ray.

Mortality. There were 11 deaths in our series of 195 cases, representing a gross mortality of 5.6 per cent. A brief clinical summary of the 11 fatalities follows:

Case Reports

Case 1. The patient was 70 years old, and the acute bleeding episode was controlled by the third day. He had arteriosclerotic heart disease with auricular fibrillation, developed pneumonia on the twenty-first day and died on the thirty-second day. Autopsy revealed a healed duodenal ulcer.

Case 2. The patient was 41 years old and had been hospitalized (in a private hospital) for bleeding for two weeks before admission, but had received no blood transfusion. The admission red blood cell count was 1.1 million. He received intravenous fluids and was receiving whole blood when he died two hours after admission. Autopsy revealed a penetrating posterior duodenal ulcer with erosion and rupture of the pancreaticoduodenal artery.

Case 3. The patient was 59 years old and gave a history of melena for two weeks. He received seven pints of blood in four days but was operated upon because of continued bleeding. He died three hours following operation. At operation a duodenal ulcer was found, but it was not actively bleeding. However, the intestinal tract was filled with blood. No autopsy was performed.

Case 4. The patient was 52 years old. He had been treated with large doses of bismuth and paregoric for six months prior to admission because of chronic diarrhea. His bleeding had already stopped by the second day, but on the fourth day he developed a fecal impaction which later caused perforation of the cecum and secondary peritonitis. He was operated upon the ninth day but died one hour later. Autopsy revealed two small gastric ulcers with evidence of recent hemorrhage.

Case 5. The patient was 59 years old and was admitted for treatment of diabetic gangrene of the left foot. He developed hematemesis on the twenty-first day, became comatose and remained so until his death on the thirty-second day. He was in shock due to hemorrhage several times, despite his receiving four pints of plasma and 18 pints of blood in this 11 day period. He also developed pneumonia on the second day of his bleeding. Autopsy revealed a gastric ulcer with evidence of recent bleeding.

Case 6. The patient was 73 years old and had been hospitalized for 10 months for arteriosclerotic cardiovascular disease and uremia. He was comatose and considered moribund at the time the bleeding started. His general condition was too poor to allow operation and he died in five days, although he had received 16 pints of blood. Autopsy revealed a gastric ulcer with evidence of recent bleeding.

Case 7. The patient was 57 years old. He was admitted for chronic cor pulmonale complicated by pneumonia, and he started bleeding 24 hours after admission. Because of pulmonary edema, blood had to be given slowly, but he received 1,000 c.c. before he died, 12 hours after starting treatment. Because of his severe pulmonary and cardiac disease, surgery was not considered feasible. Autopsy revealed an ulcer of the pyloric canal with evidence of recent bleeding.

Case 8. The patient was 35 years old. Before this bleeding episode the patient was operated upon for a chronic gastric ulcer, but technically it was impossible to resect the stomach because of the presence of a severe advanced chronic pancreatitis. Accordingly, no definitive operative treatment could be done. Massive bleeding occurred five days after operation, and because of the previous operative findings the patient was treated medically. Bleeding was controlled after two days but then recurred on the seventh day. He received a total of 13 pints of blood but died on the eighth day. Autopsy revealed a gastric ulcer with a large eroded vessel in the base.

Case 9. The patient was 58 years old and was admitted for severe hypertensive cardiovascular disease with congestive failure. He developed severe upper gastrointestinal hemorrhage while in the hospital. He continued bleeding and, although he

received 10 pints of blood, he died four days after the bleeding started. Operation was not done because of his severe cardiac disease. No autopsy was performed.

Case 10. The patient was 53 years old and was admitted with terminal bronchogenic carcinoma and chronic nephritis with massive edema. He began bleeding on the tenth day after admission, and this was controlled within the first 24 hours on conservative therapy. He died 39 days later from renal failure and pulmonary edema. No autopsy was performed.

Case 11. The patient was 56 years old. His bleeding was controlled by the second day, and he was apparently having an uneventful convalescence when he developed pneumonia and died on the twelfth hospital day. Autopsy revealed an extensive pneumonia and a healing gastric ulcer with no evidence of hemorrhage.

From these case histories, it is seen that nine out of the 11 patients who died were over the age of 50. In four (cases 1, 4, 10 and 11), the gastrointestinal hemorrhage had been controlled for at least seven days, and there was no evidence of a recurrence of bleeding at the time of death. Two of these deaths (1 and 10) were attributed to preëxistive diseases, and the other two (4 and 11) to complicating diseases.

Death was attributable to exsanguinating hemorrhage in seven cases (2, 3, 5, 6, 7, 8 and 9) (3.6 per cent). Three of these patients (6, 7 and 9) were severely ill from preëxisting diseases for which they had been admitted to the hospital. In addition, although it was known that medical management was failing to control their bleeding, they were too sick to permit surgical intervention.

Since it usually has been customary to classify the severity of bleeding according to the level of the red cell count, and since there developed in our minds some question as to the accuracy of such a concept, we made a study of the deaths in relationship to the red cell levels. It developed that of the 140 cases with counts of 3.0 million or under, there were nine deaths (6.4 per cent), and of the 82 cases with a red cell count of 2.5 million or under, there were six deaths (7.3 per cent). Thus it would seem that red cell levels, per se, are not necessarily a good indication of the severity of bleeding. Furthermore, had we chosen 3 million, or even 2.5 million, as the arbitrary upper limit for our studies, there would have been no great increase in the mortality rate.

The mortality rate in the group of gastric ulcers (31.6 per cent) was more than 12 times as high as that of the duodenal ulcers (2.6 per cent). In the group due to undetermined cause, the mortality rate was 4.3 per cent, and in the hypertrophic gastritis and other groups it was 0 per cent.

Advanced age and arteriosclerosis were two factors which definitely increased the mortality. The mortality rate for patients over 50 years of age was 11.4 per cent, and for those under 50 was only 1.7 per cent. The mortality rate for patients having arteriosclerosis as an associated disease was 16.1 per cent, compared to 3.7 per cent for those who did not have this disease.

There were 11 patients who had recurrences of bleeding while still in the hospital, and one of these died. This patient (case 8) was the man

who had had operation prior to the bleeding episode and in whom it had been impossible technically to resect his large gastric ulcer.

There was one surgical death in the 23 cases operated upon for continued or recurrent bleeding or a complication of the ulcer itself, which gave a mortality rate of 4.4 per cent. The other surgical death was following an operation for a ruptured cecum, which we considered a complication of the treatment.

Discussion

It is difficult to make accurate comparisons with other work of this character that has been published, because of variations within individual patterns of therapy, and also because of our inability to evaluate properly the conditions under which the various groups were treated. There is also quite a difference in the criteria for the selection of cases and for the classification of severity of hemorrhage. Insofar as we are capable of judging, however, our results compare favorably with any of those reported.

For whatever good results we may have obtained, we are indebted to many outside of our own service. Dr. Harold Gordon, Chief of the Laboratory Service, and his associates have worked untiringly to procure the large amount of blood which we have used, or kept available for use, in these cases. We wish to acknowledge this and to thank them and the Louisville Red Cross Blood Center for their invaluable assistance.

Also, as has already been stated, we have worked in close coöperation with the surgical service in the management of these cases. We conceive of our relationship as being essentially that of a team in which both services follow these cases from the time of admission until the bleeding has been controlled and the patient discharged. From the time of admission, as long as medical management is felt to be effective, it is under the supervision of the medical service. If and when it becomes apparent that medical management is inadequate, then the responsibility and supervision of the management are shifted to the surgical service. It would follow that, as an integral part of the team, they would share with us the credit for any results we may have obtained. This, however, would not be a full appraisal of their contribution. By the pattern of our management, it is evident that only the more difficult problems came under their responsibility. Specifically, of the 13 cases which were operated upon because of the failure of medical management to control the bleeding, five were patients who were actually in shock, and there were six others whose condition was considered poor. That Dr. Joseph Hamilton, Chief of the Surgical Service, and his associates were able to perform their surgery on these 13 patients with the loss of only one case bears testimony to the effectiveness of their management.

As to the appraisal, in retrospect, of our pattern of therapy, we are convinced that it is rational and effective. We believe that rest flat in bed, the use of antacids and a mixture of milk and cream, day and night, and the liberal use of blood transfusions constitute the foundation of medical therapy for upper gastrointestinal hemorrhage.

With some exceptions, which will be noted, we believe that these patients should be treated medically, and that operation should be resorted to only if medical treatment fails. We have no rule-of-thumb to determine whether medical measures are adequate. The patients must be considered individually. In the absence of contraindications, we believe that operation should be resorted to, even in the first few hours, if there is evidence of continued massive bleeding such as would be shown by difficulty in improving or maintaining the blood pressure by continuous or frequent transfusions. Also, assuming the patient to be a satisfactory surgical risk, we believe that operation should be performed if the patient has been subject to repeated hemorrhages, if the bleeding is coming from a gastric ulcer, if the patient is in the older age group, or if there exist other indications for operation, such as perforation, obstruction not correctable by medical treatment, or a history of a proved ulcer which has been refractory to medical management.

One of our greatest dissatisfactions is concerned with our inability to determine accurately, in many cases, whether the patient is actively bleeding and, if so, how much. It has been shown [20] on experimental animals that one-sixth to one-quarter of the total blood volume may be lost, if the animal is in the supine position, without appreciably affecting the pulse or blood pressure. The behavior of some of our patients lends support to this observation. The unreliability of the red cell count and hemoglobin determinations, as an indication of the severity of hemorrhage, has long been recognized, especially during the first few hours following the hemorrhage. Our studies lend support to this concept. If there were an accurate way of determining earlier that a patient is actively bleeding, and to what degree, thus providing more time to do something about it, one of the worst obstacles in the management of these cases would be eliminated. We have entertained the idea of placing the patients semi-upright, at about a 45° angle in bed, once they were out of shock and the pulse and blood pressure were stabilized, in the hope that it would make the pulse and blood pressure a more sensitive indicator of further bleeding. However, such a procedure would increase the blood pressure, thereby increasing the chance of aggravating the hemorrhage, and we have been reluctant to try it. We also have in mind the use of blood volume determinations, in the hope that this might add to the accuracy of our evaluation of the bleeding episode.

We are also concerned by the problem of constipation in these patients. It is a definite annoyance to both the patient and the physician, and, as two of our cases have shown, may have serious consequences. We have preferred not to use laxatives, feeling that it was preferable not to stimulate the intestinal tract and that, with diligence on the part of the physician, the lower bowel elimination could be taken care of satisfactorily by the use of enemas. We still believe this to be true, but it may be that the choice of a different antacid or the judicious use of laxatives would be a better solution to the problem.

Summary and Conclusions

1. A review has been presented of 195 cases of severe upper gastrointestinal bleeding which were treated over a five-year period at the V. A. Hospital, Louisville, Kentucky.

2. The regimen of medical management for these cases included antacid therapy and a milk and cream mixture at frequent intervals on a 24 hour basis, plus early whole blood transfusions sufficient to counteract shock or to bring the red blood count to 3.5 million or slightly above.

3. Of the 195 cases, 23 received early or emergency surgery, 13 of which were operated upon for continuing bleeding which was not being controlled satisfactorily under medical management.

4. There were 11 deaths (5.6 per cent) in the 195 cases. Of these, there were seven cases (3.6 per cent) in which death was due to uncontrolled hemorrhage. In three of these seven patients, the bleeding occurred as a complication of a severe preëxisting disease. Brief clinical abstracts were presented on the 11 patients who died.

5. As a result of our observations it is felt that, in general, and in the absence of contraindications, operation is indicated in acute severe upper gastrointestinal hemorrhage, of the type described, under the following conditions:

a. When medical treatment is not effective.

b. If the patient is past 50 years of age.

c. If the bleeding is coming from a gastric ulcer.

d. If there are other indications for surgery, such as perforation, pyloric obstruction, repeated hemorrhage or a history of a proved ulcer which has been refractory to medical management.

6. Some of the problems associated with the management of upper gastrointestinal hemorrhage have been discussed, particularly those which relate to bowel elimination and to the difficulties incident to the accurate determination of the presence and degree of active bleeding.

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PYELONEPHRITIS LENTA *

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Introduction

The clinical entity, "malignant hypertension," and the pathologic lesion called "malignant nephrosclerosis" have for a long time been ill defined and poorly understood classifications which have served as waste-baskets. Into the first have been thrown all cases of hypertension with uremia without recognizable cause, while the second has received every kidney showing petechiae and arteriolonecrosis. After a study of the renal lesions found in a large series of cases of so-called malignant hypertension, we believe that specific anatomic lesions, though multiple, are quite distinct and in almost every instance identifiable. We also found that these lesions are often clinically evident and separable etiologically. Finally, we concluded that an overwhelming majority of cases were caused by severe chronic nondestructive pyelonephritis.

Historical Survey

Malignant hypertension was first separated as an entity by Volhard and Fahr [1] in 1914, who described it as an arteriosclerosis with a superimposed acute glomerulonephritis, and termed it a "combination form" of Bright's disease. Shortly after this, the inflammatory element of the disease was denied by Jores [2] and Löhlein,[3] who attributed the glomerular lesion to rapidly occurring ischemia consequent to severe arteriosclerosis. Later, both Volhard [4] and Fahr [5] reversed themselves, the latter coining the term "malignant sclerosis." He suggested a toxic cause for the endarteritis and necrosis of the arterioles. Kieth, Wagener and Kernohan [6] emphasized the widespread arteriolar involvement, described the characteristic retinitis and named the disease "malignant hypertension." With the exception of the classic work by Goldblatt on ischemic renal hypertension, little progress has been made in clarifying the etiology and pathogenesis of the disease. Most authorities [7, 8, 9, 10, 11, 12, 13, 14] have accepted Fahr's explanation, that the disease is merely a variant of renal arteriolosclerosis with terminal arteriolonecrosis. Many have reserved a special position for that type which occurs in the youngest age group, runs a rapid course, and eventuates in larger, smoother kidneys with much less scarring.

Most of the standard texts and pertinent articles refer to malignant nephrosclerosis as synonymous with malignant hypertension. Yet, though

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these terms are almost universally used, there is no consistent description of a single morphologic entity. Grossly, the kidneys are variously described as markedly contracted, normal in size or slightly enlarged. The surface varies from smooth to finely granular, to coarsely granular, or scarred. Usually it is red, and, almost uniformly, smaller or larger hemorrhages are mentioned. The microscopic descriptions are just as confused, some authorities stressing glomerular changes, others tubular damage, and still others, changes in the interstitial tissue. Only a single common feature is found by all—arteriolonecrosis. Table 1 is a summary of a few of the

TABLE I

Description of Malignant Hypertension (Nephrosclerosis) by Various Authorities

Authority	Kidney in Gross			Microscopic Appearance
	Size	Hemorrhages	Surface, Scars, etc.	
Klemperer and Otani[17]	Small (average, 113 gm.)	Bright petechiae in every case	Diffusely granular with flat brown elevations above slightly depressed areas. Few deep scars	Marked interlobar artery sclerosis. Arteriolar necrosis. Nonspecific glomerular changes with tubular degeneration
Fishberg[12]	Normal or slightly swollen, occasionally contracted	Hemorrhages of varying size and irregular outline	Slightly granular or well-marked granulations. Brown or grayish-red, variegated by yellowish areas	Nephrosclerosis with necrosis and endarteritis of interlobular, afferent and glomerular vessels
Bell[18]	21% normal, 30.5% severely contracted	Not mentioned. (Thrombonecrosis found microscopically in 65%)	Contracted in 79%	Severe sclerosis of small arteries and arterioles. Thrombonecrosis in 65%. Focal glomerulitis in 35% (considered a characteristic finding)
Muir[19]	Usually normal	Ill-defined reddish areas or spots	Surface uneven but usually not definitely granular	Arteriosclerosis with multiple minute infarcts
Boyd[13]	Normal, slightly enlarged or contracted. May differ in size	Usually large hemorrhages, sometimes small	Smooth surface if normal size; granular surface if contracted	Benign nephrosclerosis with arteriolar necrosis and epithelial crescents
Moore[2]	Normal or slightly small	Numerous punctate hemorrhages	Finely granular, firm and red. The cortex is slightly reduced	Arteriosclerosis and arteriolonecrosis with glomerular infarction and tubular degeneration
Anderson[9]	May be atrophic	Flea-bitten	No description	Acute necrotizing arteritis and arteriolitis. If malignant hypertrophy is superimposed on benign, there is arteriosclerosis

prevailing opinions gleaned from the literature and a few standard texts. It seems remarkable that the term, malignant nephrosclerosis, could have perpetuated itself in the absence of one characteristic gross and microscopic picture. One gains the impression that the adjective "malignant" was borrowed from the clinical term "malignant hypertension," and the expression "nephrosclerosis" from the arteriolar nephrosclerosis found quite often in essential or so-called benign hypertension. "Malignant nephrosclerosis" does not exist as a single, well defined disease, and such terminology should be discarded.

This study concerns an examination of the kidneys of 50 patients diag-

nosed clinically as having malignant hypertension. After careful evaluation of the renal changes (and disregarding the loose concept of malignant nephrosclerosis), it was found that the vast majority of parenchymal changes fitted the concept of chronic pyelonephritis, so well described by Weiss and Parker.[16] Superimposed upon old inflammatory changes, a more recent necrosis of some of the arterioles was found. To differentiate this type of kidney lesion from those of the "destructive" variety of pyelonephritis with hydronephrosis (pyonephrosis, abscesses and destruction of pyramids), the term "pyelonephritis lenta" was coined.

Pyelonephritic contracted kidneys had been described in the various older texts of pathology, but their clinical significance had not been recognized until Weiss and Parker's studies.[16] These authors also gave a clear-cut description of the relevant gross and microscopic changes, establishing easily recognizable criteria. The relation of chronic pyelonephritis and hypertension in general has since been pointed out on many occasions and very recently again by Dovsen, Ball and Platt.[15]

Prior to the study of Weiss and Parker, many kidneys, the seat of these changes, had been classified as chronic glomerulonephritis, and thus the rôle of chronic pyelonephritis lenta in relation to hypertension had not been fully appreciated. This fact is graphically illustrated by a perusal of our own autopsy diagnoses before and after Weiss and Parker's pertinent study. During a five year period (1935–1939) before Weiss and Parker's study, chronic glomerulonephritis was diagnosed 15 times among an autopsy population of 1,799, and chronic pyelonephritis nine times. However, during the years 1945–1949, chronic glomerulonephritis among an autopsy material of 2,234 was diagnosed only twice, and chronic pyelonephritis 47 times (chart 1).

Method

The present study was based on an examination of the kidneys from 50 patients clinically diagnosed or diagnosable as malignant hypertensives. First, certain features of the histories and gross anatomic findings were reviewed and analyzed. The microscopic slides were then reëxamined for the criteria set by Weiss and Parker, and an attempt was made to define clearly the changes of the nondestructive variety of chronic pyelonephritis or pyelonephritis lenta.

In the following, the more pertinent clinical features of patients with this type of kidney lesion will be briefly reviewed. Special attention has been paid to the arterial blood pressure, the blood chemistry findings in regard to renal failure, and the presence or absence of anemia. An attempt is also made to show how, in such instances, the anatomic diagnosis of chronic pyelonephritis of a special type can frequently be made clinically, rather than the ambiguous diagnosis of either benign (essential) or malignant hypertension. A description of the relevant renal lesions, especially those apparently causing the arterial hypertension, will also be given. An emphatic

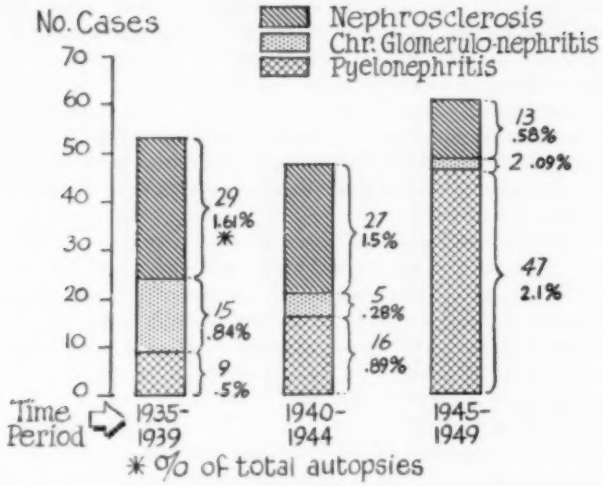

CHART 1. Uncorrected autopsy diagnoses for this 15 year period show a trend toward more frequent anatomic diagnosis of chronic pyelonephritis at the expense of chronic glomerulonephritis and nephrosclerosis.

distinction is made between this type of pyelonephritis, designated as the "lenta variety," and the "destructive variety," with pyonephrosis and erosion of portions of the pyramids and cortex.

SELECTION OF CASES

It soon became obvious that the selection of cases would be a fairly difficult procedure, since the clinical entity of malignant hypertension is a rather vague one. It was frequently associated with unrelated, though possibly modifying lesions, such as urinary obstruction with ascending infection, malignancies, infections, etc. Many cases were complicated by recent arteriosclerotic occlusions in brain and heart, or by severe heart failure. So that we might arrive at a clinical constant and not have to assess these modifying factors, we selected only those patients with hypertension dying in uremia. If patients were moribund on admission, hypertension was not required, since it is well recognized that a fall in blood pressure occurs just before death. A history of hypertension was deemed sufficient. We eliminated all instances of ascending infection due to obstruction of the lower urinary tract, such as calculi, prostatic enlargement, postprostatectomy infections, neoplastic obstruction of ureters, etc. All cases complicated by recent myocardial or cerebral infarcts, and those whose clinical picture was primarily that of heart failure, whether due to hypertensive, coronary artery or valvular heart disease, were also excluded.

Although malignant hypertension is usually conceded to be a rather rapidly progressive disease, with or without preëxisting "benign" hypertension of prolonged duration, the histories were often difficult to assess, since the patients were frequently admitted in a disoriented or comatose state. In the main, a more or less rapidly progressive course was noted. The age group is restricted by some to patients of middle age or below. However, the age factor was neglected in our selection, as it is by the majority of authorities. In all, only 50 cases met the above described criteria out of an autopsy population of 4,030 during the years 1940 to 1949.

To arrive at a basis for comparison, we chose as controls a second series of 50 patients with hypertension, all of whom had died of complications other than uremia. These complications included myocardial and cerebral infarcts and heart failure. Their clinical and anatomic features were similarly reviewed and compared statistically with the cases diagnosed as malignant hypertension. In both series the selection was of consecutive cases which met the previously mentioned criteria.

Clinical Notes

In an attempt to find a common denominator, we analyzed several of the more important clinical features of our selected cases. The average age of the malignant hypertension group was 47.7 years, as compared with the control group average of 64.6 years. This is a significant difference, quite in accord with established ideas of separating malignant hypertension as a definite entity. Sixty per cent were males and 40 per cent females, a statistically insignificant difference.

A history of definite antecedent attacks of chills, fever, pyuria, back pain, etc., was seldom obtained. This is readily understandable, since this history was not sought by the clinician, and the seriously ill patient did not volunteer the information. In any event, pyelonephritis, more frequently than usually recognized, causes few overt symptoms, and most attacks are probably unrecognized. The clinically manifest duration of the entire disease was, on the whole, below two years, a large minority noting the onset of symptoms two months or less prior to death. Another large minority gave a history of onset of hypertension dating back two to 20 years. Valid statistical data were difficult to obtain, not only because of the small number of cases but also because of inadequate histories. Only five cases (10 per cent) showed a systolic blood pressure below 200 mm. Hg or a diastolic below 100 mm. The average systolic was 227 mm. and the average diastolic was 133 mm. In the control series the average systolic was 180 mm. and the average diastolic was 102 mm.

The degree of azotemia could not be evaluated in all cases, since it was recorded variously as serum urea nitrogen and non-protein nitrogen. It was often taken either in desultory fashion or not at all, particularly when the patient survived for only a short time after admission. Of 44 cases in

which this was recorded as serum urea nitrogen or non-protein nitrogen, the figures were above 55 mg. per cent in every case, above 100 mg. per cent in 29 (or 68 per cent of the cases), and above 200 mg. per cent in 20 (or 45 per cent of the cases). Anemia was an almost constant laboratory finding. Urinary albumin varied from traces to 4 plus. Pus cells in pathologic numbers were found quite commonly. Red cells varied in numbers from absent to many. Casts of many varieties were occasional findings.

Thus the significantly diagnostic features of the group were a lower average age, systolic blood pressure above 200 mm. and/or diastolic above 100 mm., uremia, anemia, and the pathologic urinary findings. The heights of the arterial blood pressure differentiated the group of chronic pyelonephritic patients from those with chronic glomerulonephritis, in which the tension seldom reaches this level; and the constant, fairly severe anemia separates them from patients with nephrosclerosis ("essential hypertension").

Gross Kidney and Heart Findings

The average weight of both kidneys was 244 gm. in the uremic group, as compared to 322 gm. in the control series of hypertension without uremia. A difference in size of each kidney was mentioned in a considerable number of cases, despite the custom in this institution of weighing kidneys together (figure 1). In eight cases one kidney was much more involved than the

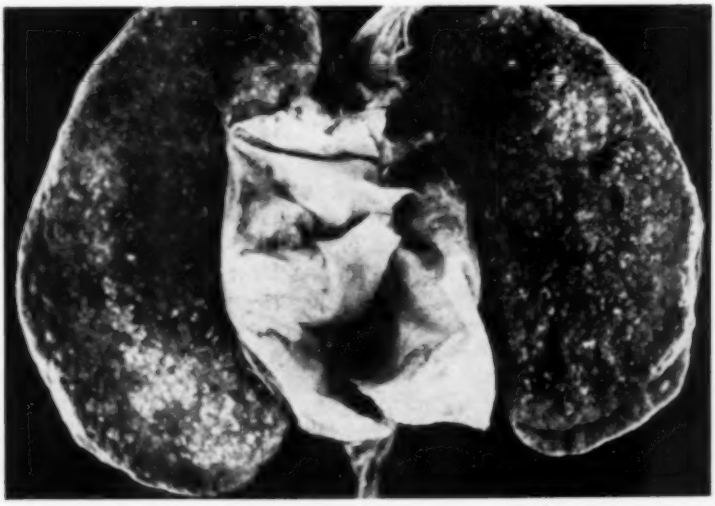

Fig. 1. The right kidney is definitely smaller. There are a bilateral, coarse nodularity and numerous large flat scars. The latter are best seen on the cut edge or tangentially. Small punctate hemorrhages are just visible.

FIG. 2. The shallow scars are well illustrated on both the flat surface and the cut edges.

opposite one. In general, the kidneys were smaller than normal and their capsules stripped off with some difficulty. The kidneys were usually described as yellowish, resembling those of chronic glomerulonephritis. Though at first sight the surfaces may have appeared smooth, there were almost uniformly present a few larger or smaller broad, flat scars which were slightly depressed beneath the surface. If the scars were large and involved a great portion of the kidney surface, they were sometimes difficult to recognize (figure 1). They became more apparent on the cut surface because of the shallow U-shaped depression they produce (figure 2). The surface of these scars was yellowish-red and, though they may have seemed smooth, on closer inspection they were either velvety or very finely granular (figure 2). Hemorrhages, usually petechiae, were mentioned in only 40 per cent of the cases, though we believe from the microscopic picture that their incidence would have been much higher if a more careful search had been made (figures 3 and 4). On section, the normal architecture of the cortex was not recognized, being thinned, usually yellowish, and containing grayish or pinkish streaks, which were also noticeable in the pyramids. Often the tips of the latter were flattened instead of cone-shaped. The pelvis was usually slightly dilated and quite often disclosed a thickened, opaque though velvety mucosa. Abscesses were never present, unless a definite acute exacerbation of chronic pyelonephritis was present.

The hearts exhibited the expected diffuse hypertrophy of hypertension, weighing, on the average, 445 gm. Often the findings were nonspecific, except for the frequent recording of a bland fibrinous pericarditis.

In summary, the kidneys were considerably reduced in size, often unequally. They were smooth or nodular, with flat granular yellowish-pink scars and scattered petechiae. The cortex was narrow, with obscured scarred architecture. The pelves were scarred and the tips of the pyramids flattened. The heart was hypertrophied, and there was frequently an acute fibrinous pericarditis.

FIG. 3. Multiple petechial hemorrhages are seen on the pale surface. The shallow scars are not well seen.

HISTOLOGIC FINDINGS

Sections of the kidney were all critically re-analyzed, in most cases the routine hematoxylin and eosin stain being used, though a few were also stained with trichrome and orcein dyes. Nine inflammatory parenchymal lesions were specifically studied, as well as five vascular lesions, as follows:

An attempt was made to grade each criterion in every case on the basis of 1 to 4 plus estimations, and when in doubt we used the lower estimate. After this a final analysis was made and a conclusion drawn, both as to the type of renal disease encountered and as to its grade, again on a 1 to 4 plus basis.

In the past few years we, as well as others (McManus,[18] etc.), have

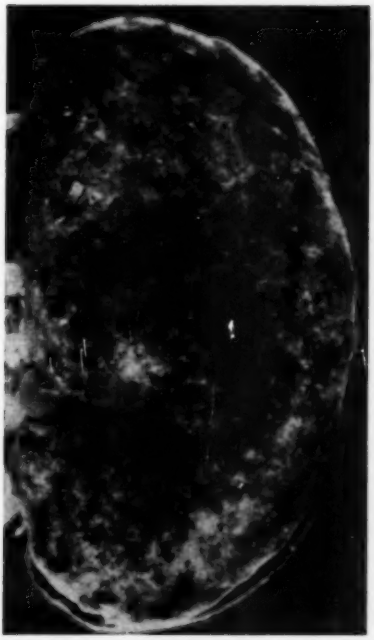

FIG. 4. Larger hemorrhages as well as the broad, flat scars are easily seen on the external surface of this kidney.

noticed in routine autopsies of patients whose death was unrelated to renal diseases the very frequent findings of small renal scars containing most of the criteria listed below and appearing with increasing frequency in older age groups. Neither the clinical history nor the gross anatomic findings

TABLE II

Microscopic Criteria Used in Judging Kidneys for Evidence of Chronic Pyelonephritis

1. Pleomorphic interstitial infiltrate
2. Tubular changes
   a. Dilatation by colloid casts with flattened epithelium
   b. Atrophy
   c. Inflammation within tubules
3. Glomerular lesions
   a. Concentric periglomerular fibrosis
   b. Alterative glomerulitis
   c. Fibrosis and hyalinization of glomeruli
4. Chronic pyelitis and renal capsular scarring
5. Vascular lesions
   a. Arteriosclerosis or healed arteritis of interlobar arteries
   b. Arteriosclerosis or healed arteritis of interlobular arteries
   c. Diffuse hyperplastic sclerosis of arterioles
   d. Fibrohyaline change in arterioles
   e. Thrombonecrosis of arterioles

gave any clue to the etiology of these scars. We have interpreted them as focal chronic pyelonephritis and have concurred in the opinion that they are the result of unrecognized minimal attacks of a really quite ubiquitous disease which, in most cases, causes no significant renal disturbance. We eliminated these from our data as the cause of the hypertension, only the diffuse disease being retained. This was occasionally difficult when only one or two small blocks of kidney could be examined.

I. Interstitial Infiltrate

In most cases, the inflammatory exudate in the interstitial tissue was of a pleomorphic nature, consisting of lymphocytes, plasma cells, histiocytes

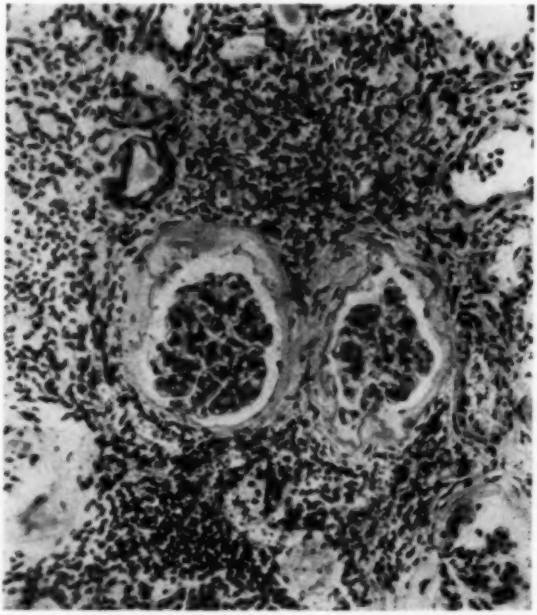

Fig. 5. Concentric periglomerular fibrosis. Note the atrophic tubules and profuse interstitial exudate. Occasional tubules are dilated. Hematoxylin and eosin stain. × 140.

and occasional eosinophils (figure 5). When the lesion was acute there was a predominance of polymorphonuclear leukocytes, with a typical involvement of the periglomerular lymphatics, and occasional perivascular concentration simulating periarteritis nodosa. As the activity died down this was gradually replaced by histiocytes, plasma cells, lymphocytes, a few eosinophils and young fibrocapillary tissue. Later on, lymphocytes became the pre-

dominant feature, with a few plasma cells and histiocytes, and a rare eosinophil. Finally, in the quiescent phase, interstitial fibrosis became the prominent lesion and, while lymphocytes were found in fairly large numbers, plasma cells and histiocytes were quite sparse and eosinophils absent. Since this last state is also found in chronic glomerulonephritis, in the replacement fibrosis of nephrosclerosis, in old infarcts, etc., it was rather difficult to evaluate. Therefore, a diagnosis of chronic pyelonephritis was not made

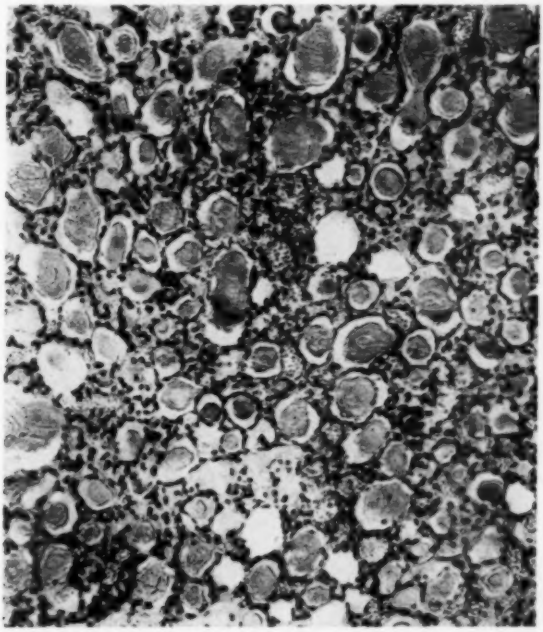

FIG. 6. Thyroid-like tubules filled with colloid casts. Hematoxylin and eosin stain. × 100.

in the absence of more characteristic criteria. A significant (2 plus or better) chronic pleomorphic infiltrate was found in 88 per cent of cases.

II. TUBULAR CHANGES

A. "Colloid casts," which were very often present, were the result of dilatation of the convoluted tubules and loops of Henle, with flattening of the epithelium and deposition of refractile eosinophilic "casts." When they were seen in such profusion as to give a thyroid-like picture, they were considered quite characteristic of chronic pyelonephritis (figure 6). They were not found in the acute stages of pyelonephritis. Occasional colloid

casts in dilated tubules were also found in the scarred areas of arteriosclerosis and glomerulonephritis. Therefore, when they were sparse and scattered, they were not used as confirmatory evidence in the final histologic diagnosis. Moderate to large numbers of colloid casts were found in 66 per cent of the cases, compared to only 4 per cent of the controls.

B. Small atrophic tubules were perhaps just as frequent a finding as those dilated by colloid casts, but since they are nonspecific lesions found in the fibrotic areas of both degenerative and inflammatory diseases they could not be used as one of our criteria (figure 8). Occasionally these were the most prominent tubular feature, colloid casts being inconspicuous.

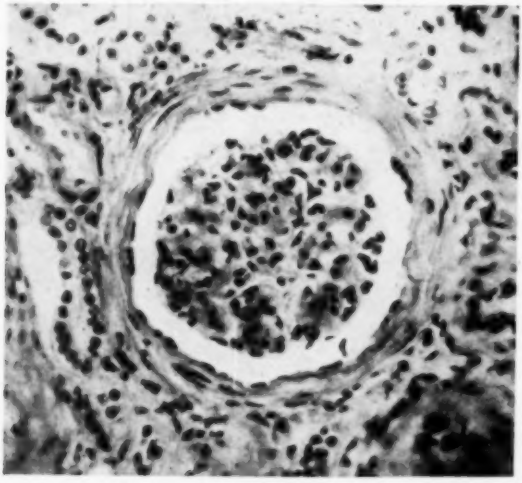

FIG. 7. Concentric periglomerular fibrosis. Hematoxylin and eosin stain. × 280.

C. Inflammatory cells within the tubules in the form of polymorphonuclear leukocytes were a quite common finding. Whether this was indicative of activity of inflammation or merely the result of the irritating influence of noxious material in the colloid casts is difficult to say, since they were occasional findings even in the dilated tubules of "burnt out" pyelonephritis. In the acute stages or acute exacerbations of chronic pyelonephritis, they were found in profusion filling the tubular lumina and forming casts. Thus, their value in the diagnosis of acute pyelonephritis was great, while their significance in the chronic stages was of much less importance. In our series, 42 cases (84 per cent) had acute inflammatory cells within tubules, as opposed to only one in the controls (which showed only 1 plus inflammatory cells).

III. Glomerular Lesions

A. Concentric periglomerular fibrosis was a fairly characteristic and constant finding, due to the organization of the periglomerular polymorphonuclear infiltrate of the acute stage. It was always extracapsular and, as such, readily distinguished from the crescents of glomerulonephritis (figures 5 and 7). Occasionally demilunes were also found in association with the periglomerular fibrosis, probably as the result of organizing intracapsular hemorrhages due to arteriolonecrosis and not as the result of a primary

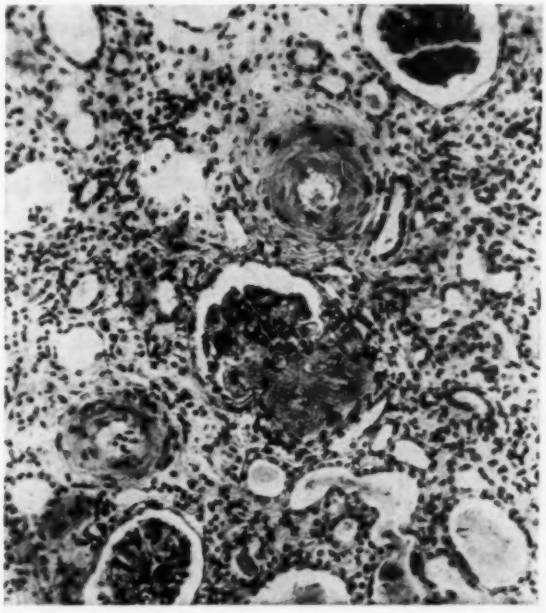

Fig. 8. Arteriolar necrosis of afferent arteriole extending into glomerular capillaries. The two interlobular arteries show "onion-skin" intimal proliferation, with marked luminal narrowing. Note also the interstitial infiltrate, the dilated and atrophic tubules, and the lack of involvement of the glomeruli. Hematoxylin and eosin stain. ×140.

glomerulitis. Difficulty was seldom experienced in differentiating this periglomerular lesion from the diffuse fibrosis found in the very common tiny cortical arterial scars and in larger organized infarcts. It must again be emphasized that with advancing age, small chronic pyelonephritic scars become almost universal, and that, therefore, occasional foci will contain periglomerular scarring. However, if sufficiently large areas are examined, this factor can usually be eliminated.

In the series of kidneys of "malignant" hypertension, 84 per cent of cases showed this type of fibrosis, over 50 per cent being of severe degree. In the controls, only 24 per cent showed the periglomerular fibrosis, most being of slight degree and usually present in small pyelonephritic scars.

When large numbers of polymorphonuclear leukocytes were found in periglomerular locations, this was interpreted as an indication of acuteness or acute exacerbations of the inflammation.

B. Alterative glomerulitis or an increase of cellularity of the glomerulus, due both to endothelial proliferation and to polymorphonuclear leukocytic infiltration, was a factor which, like the periglomerular polymorphonuclear leukocytic infiltrations, was indicative of the activity of the lesion. This was occasionally difficult to distinguish from the glomerular reaction to capillary necrosis. It was found to a slight extent in 22 per cent of the uremic series, and to a moderate or severe degree in only 4 per cent. In the control series it was seen only three times, two cases being slight and one moderate.

C. Fibrosis and hyalinization of glomeruli are completely nonspecific lesions, being found in all scars, whatever their etiology. We attempted a rough estimation of the reduction in the functioning renal parenchyma to see whether there was a significant difference in the degree of renal atrophy in pyelonephritis versus that found in arteriosclerosis. Since in most cases only small segments of kidney were taken for section, and the size of the section had little correlation to the size of the kidney, the estimations were quite approximate. In the "malignant" series, all showed a significant amount of glomerular fibrosis, 40 per cent of cases showing more than 40 per cent scarred glomeruli, while in the control series only 4 per cent showed over 40 per cent of the glomeruli scarred. This is an expected difference in patients dying of uremia as compared to those dying of other complications of hypertension.

In general, one of the most significant findings was the fact that, even on very superficial examination, the changes in the interstitial tissue and tubular apparatus were much more severe than the changes in the glomeruli. Because the scarring involved both convoluted tubules and interstitial tissue, with their resultant shrinkage, the glomeruli appeared proportionately more numerous. Thus the impression of more than the expected numbers of glomeruli in microscopic fields showing little more than interstitial fibrosis lends added proof to a diagnosis of chronic pyelonephritis.

IV. Chronic Pyelitis and Capsular Scarring

These criteria could not be evaluated in many of the cases. The capsule was frequently absent, because of the habit of stripping it from the cortex before taking sections, and sections of the pelvis were not taken in every case. When a section of pelvis was available, it generally showed evidence of old inflammation in the form of fibrous thickening, chronic inflammatory

infiltrates, and foci of pyelitis cystica or, more rarely, pyelitis granularis. Our statistics indicated a significant degree of inflammation in 24 out of 27 cases (82 per cent), while the control group of hypertensives showed this in only eight out of the 34 cases (24 per cent). Evidence of capsular inflammation and scarring was difficult to interpret, since some lymphocytic infiltration and fibrous thickening are present in areas of capsule regional to cortical scars of all types. Our statistics did, however, point to a more severe and more constant inflammatory scar in the "malignant" group, among which 20 out of 25 cases (80 per cent) exhibited significant changes. In the controls, only five out of 35 (14 per cent) showed these changes.

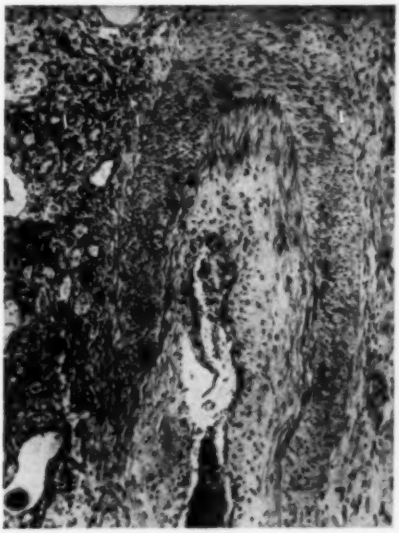

FIG. 9. Interlobar artery with arteritis deformans. Note the marked, irregular, knoblike intimal proliferation. Hematoxylin and eosin stain. × 40.

V. VASCULAR CHANGES

The vascular changes were particularly studied in an attempt to find qualitative as well as quantitative changes that might account for the difference in the clinical picture. We also examined the arterial lesions with reference to their location as interlobar, arcuate and interlobular arteries, again in an attempt to further localize a diagnostic lesion.

A. The interlobar arteries were located microscopically as large vessels in the pelvis or the medulla up to the corticomedullary junction. The lesion encountered in most instances was an intimal fibrous or fibrohyaline thickening, with or without medial hypertrophy. This thickening was often so

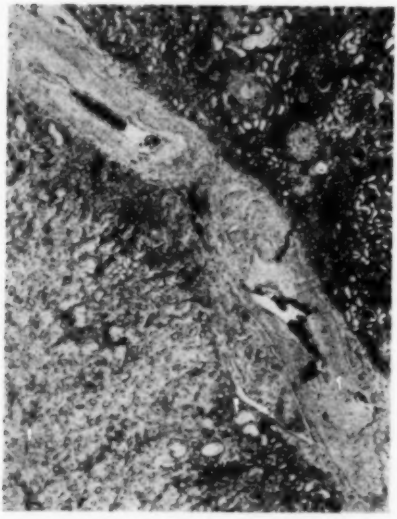

FIG. 10. Interlobar artery showing arteritis deformans in a scarred kidney. Hematoxylin and eosin stain. ×15.

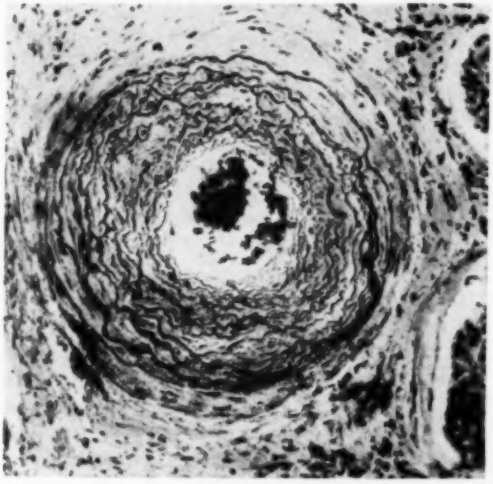

FIG. 11. Interlobular artery. Note the marked splitting and reduplication of the elastic lamellae. Orcein stain. ×140.

marked that it immediately suggested severe degenerative arteriosclerosis, despite the frequent absence of correlation with the age of the patient. Sometimes intimal cellular proliferation in an isolated area was noted projecting knoblike into the lumen. Often circumscribed areas of projecting intimal fibrosis suggested a rapid change from cellular proliferation to fibrosis. As a result of apparently older changes, the lumens of the involved arteries not only became narrowed but, because of the irregular deposition of connective tissue, were also markedly deformed (figures 9 and

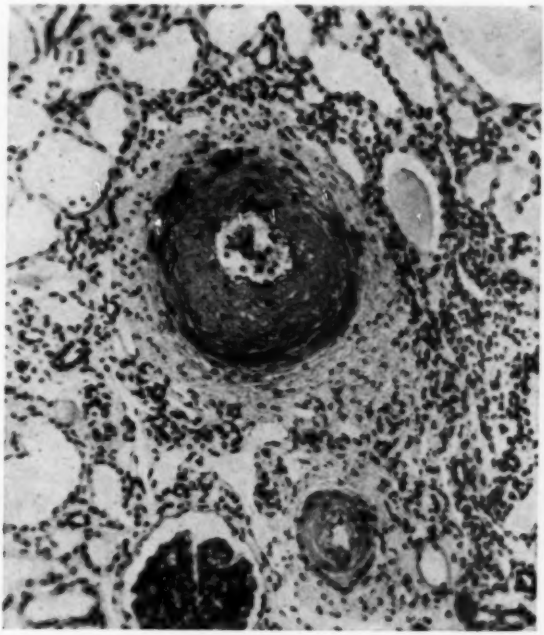

FIG. 12. Small and large interlobular arteries, showing marked intimal and medial hyperplasia with luminal narrowing. Note the typical, dilated, cast-filled tubules and interstitial infiltrate. Hematoxylin and eosin stain. ×140.

10). In still later instances, the newly formed intimal connective tissue characteristically became slightly basophilic, with areas suggesting myxomatous changes. Fatty deposits in the proliferated intima were rarely noticed. The internal elastic laminae were often thickened and split into several thick, isolated lamellae. From the above, it seems that these changes probably are not the result of a primary arteriosclerosis confined to the kidney. The vascular changes should be classed as "deforming arteritis," the result of the primary inflammation of the connective tissue in these

kidneys. The interlobar vessels showed these changes in 2 plus or greater degree in 82 per cent of cases, as contrasted with 34 per cent of the control series.

B. The interlobular arteries were those found in the cortex and, since the changes did not differ significantly from those found in the arcuate arteries at the corticomedullary junction, the latter were included in this group. The intimal changes were uniformly more severe than those seen in the interlobar arteries. Because of their smaller size, their lumens were also relatively much more narrowed, but deformed lumens were not so

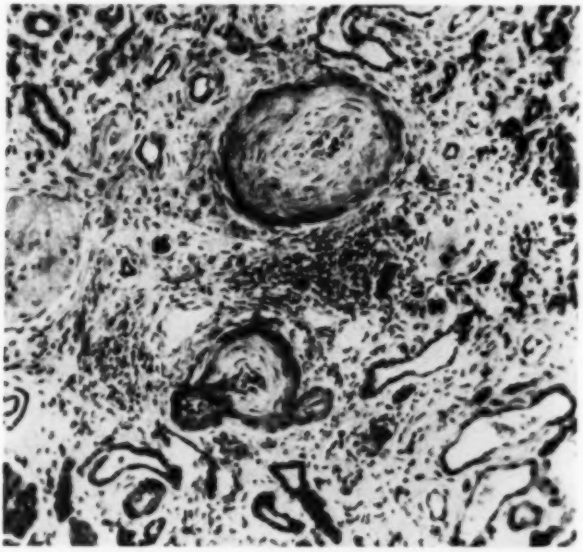

FIG. 13. Interlobular arteries with almost complete obliteration of lumens by intimal proliferation. This looks violet in H&E stain. Note the origin of two small hyalinized arterioles from the smaller artery. Hematoxylin and eosin stain. × 140.

noticeable (figures 8, 12 and 13). The media often showed a marked hypertrophy and multiplication of the elastic lamellae (figure 11). Of the uremic group, 82 per cent exhibited this lesion in 3 or 4 plus degree, while the nonuremic controls exhibited this extent of change in only 26 per cent of the cases.

C. Arterioles: Only those vessels were considered arterioles which were of the size of the afferent or efferent vessels. Normally, arterioles are fairly inconspicuous in kidney sections, and sometimes they are found only after carefully searching several fields. They become more prominent in scarred areas, whether these are focal or diffuse. When changes were found only

in focal scars, their significance in the general renal picture was discounted.

1. Diffuse hyperplastic sclerosis of the arterioles was without doubt the most common lesion found, occurring uniformly in every instance. Microscopically, it consists of a typical cellular onion-skin proliferation of the wall, with marked luminal narrowing (figures 8, 12 and 13). Since it was just as constantly present in the control group, it offered little aid in differentiating the two. Quantitatively it was of 3 or 4 plus grades in 92 per cent of the uremic cases, and in similar grades in 48 per cent of the nonuremic group. If it is true that this type of arteriolar sclerosis is secondary to prolonged

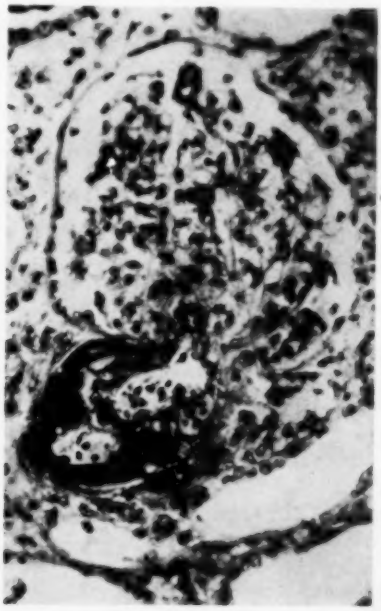

FIG. 14. Arteriolar necrosis of an afferent arteriole. Note the smudgy appearance. Hematoxylin and eosin stain. × 280.

hypertension, the difference in incidence of the more severe lesions may be due to the almost uniformly higher arterial tension in the "uremic" group.

2. The fibrohyaline changes are those in which the arteriolar wall becomes converted into a densely eosinophilic refractile mass with sharply defined edges. The lining endothelial cells and nuclei, however, are still clearly recognizable (figure 13). This lesion seemed nonspecific. It often caused a marked narrowing of the lumen but seemed unrelated to regional inflammatory disease, except by coincidence. There was no significant

difference in frequency or severity of this lesion in the "malignant" versus the control group.

3. Arteriolar necrosis was easily distinguishable from the fibrohyaline changes by the smudging of the necrotic walls, the absence of clearly defined mural and intimal nuclei, and the presence of red blood corpuscles and fibrin (figures 8 and 14). It was found in the glomerular capillaries (capillary thrombonecrosis) even more commonly than in the arterioles (figure 15). In the former, it was associated with erythrocytes and fibrin in Bowman's capsule. It also seemed that beginning organization of this hemorrhage

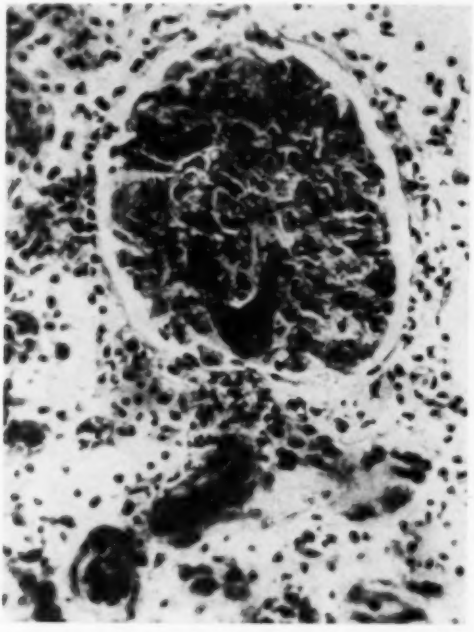

FIG. 15. Arteriolar and capillary necrosis. Hematoxylin and eosin stain. × 280.

simulated somewhat the crescents of glomerulonephritis. Frequently, also, the necrotic lesions were quite scarce and required careful search of multiple blocks. They were found in 74 per cent of the "malignant" cases, as well as in two cases (4 per cent) of the controls. Both of the latter had mild azotemia, in addition to a cerebral infarct in one and a myocardial infarct in the other. It would seem that if multiple blocks could be examined in the uremic cases, the percentage would be still higher.

The arteriolonecrosis in most of these kidneys was obviously of very recent duration, since there was no cellular reaction of any type noticeable.

This "dead" necrosis was found both in those instances in which uremia was present for some time and in those in which uremia was in evidence clinically only shortly before death. The type of necrosis of the arterioles did not vary with the duration of the uremia. From the histologic appearance of the vessels, and especially from the absence of significant cellular reaction, it seems inconceivable that these changes could possibly have antedated the onset of uremia. Neither could they then have been the cause of the uremia or of the so-called "malignant phase" of hypertension.

Summary of Histological Findings

Although no single microscopic criterion was in itself sufficient to separate the cases into groups, when the relative degree of involvement of all the criteria, as determined objectively and without recourse to either history or gross findings, was assessed, a definite diagnosis could be made in almost every case. Among the 50 cases diagnosed clinically as "malignant hypertension," we found that 43 were the seat of moderately severe to severe chronic pyelonephritis (2, 3, and 4 plus). In six instances, the chronic pyelonephritis was only slight (1 plus), and probably not the cause of the uremia. Three of these cases disclosed as their primary lesions arteriosclerosis and arteriolosclerosis, while the remaining three showed severe acute pyelonephritis. There was only one case which did not manifest any evidence of chronic pyelonephritis, and this was diagnosed as arteriolar nephrosclerosis with arteriolar necrosis.

Discussion

Just as we have seen the etiologic rôle of chronic pyelonephritis in hypertension grow in importance, so it seems clear from the foregoing findings that it exists as the lesion of primary importance in most cases of malignant hypertension. Grossly, the change that it produces is usually readily recognized and the microscopic lesions are quite characteristic. The severe changes in the interstitial tissue and tubular apparatus, as contrasted with the minimal glomerular damage, are a particularly constant observation. Severe vascular changes are uniformly present, and of particular importance are those of the arteritis deformans variety. Necrosis of the arterioles is a late occurrence. These lesions constitute a variety of pyelonephritis which, in addition to being an anatomic entity, is probably also a clinical one. There is usually no history of urinary infection or obstruction. A history of pyelonephritis during pregnancy or a definite attack of pyelonephritis years back is a distinct rarity. Thus, in its course the disease resembles the slowly progressive one of chronic glomerulonephritis without an antecedent history of an acute episode. It has an insidious onset unrecognizable till the patient presents the symptoms of essential hypertension, which often culminates in rapidly developing renal failure. This is the type of pyelo-

nephritis which has been extensively studied by Weiss and Parker and which we have termed "pyelonephritis lenta."

In contradistinction to this form of chronic pyelonephritis is the destructive variety. Here one finds an obvious cause of urinary obstruction either from the history or at autopsy. There is usually a dilatation of the ureters and pelves, with evidence of destruction of the kidney parenchyma. An ascending infection results in pyonephrosis and pyelonephritic abscesses, with further erosion of kidney substance, culminating in saclike kidneys. Though these kidney lesions were not the subject of this investigation, we feel that they usually do not result in hypertension; this is particularly true of the saclike kidneys, where the parenchyma is almost completely destroyed. In rare instances, when there is relatively little renal destruction but more severe endarteritic changes, hypertension may follow. Thus, though ischemia may be the cause of renal hypertension, the mechanism requires the presence of adequate quantities of renal parenchyma.

The most important clinical symptom of pyelonephritis lenta is the arterial hypertension with systolic pressure above 200 and diastolic above 100 mm. Dovsen, Ball and Platt [15] stress the fact that symptoms and signs of urinary infection may be completely absent when the patient is seen in an advanced stage. They emphasize the usual absence of positive urine cultures and even albuminuria, though the latter is fairly constant in the uremic stage. The remaining urinary findings may be insignificant. An almost constant anemia is present. There are instances in which the blood chemistry findings are normal. In 50 per cent of our cases, patients with apparently quiescent pyelonephritis of long standing developed either a superimposed acute pyelonephritis or an exacerbation of their old lesion. This additional insult to already damaged kidneys resulted in rapidly progressive renal failure and the syndrome of "malignant hypertension." In our opinion, chronic pyelonephritis predisposes the kidney to acute pyelonephritis more than any other renal lesion, and this sequence is the most common cause of "malignant hypertension." Demands for increased renal output found in inflammatory disease, such as bronchopneumonia, or interference with the already impaired blood supply of the kidneys, as seen in progressive heart failure, are other examples leading to the rapidly fatal uremia called malignant hypertension.

It is obvious that, since the only constant finding of the pre-uremic stage of pyelonephritis is hypertension, some of the patients may succumb to the same terminal events found in essential hypertension (arteriolar nephrosclerosis), myocardial failure or thrombotic vascular occlusions. As a matter of fact, in our control group of 50 cases diagnosed as essential or primary hypertension there were eight patients with chronic diffuse pyelonephritis of the lenta variety. These died of myocardial or cerebral infarcts or of heart failure. Similarly, in most of the cases of unilateral pyelonephritis with hypertension which have been reported in the literature, the pyelonephritis

seemed to be of the lenta variety. In 62 per cent of the patients of our uremic series, the clinical diagnosis of essential hypertension was made before the onset of renal failure.

The mechanism of the arterial hypertension in this disease lends itself readily to the Goldblatt explanation. As has been shown, the interstitial inflammation of pyelonephritis extends to the intrarenal vasculature, producing at first acute lesions resembling panarteritis, and progressing to scarring with narrowed deformed arterial lumens. Though microscopically the latter stage resembles arteriosclerosis, the process is really an "arteritis deformans." The narrowing which is anatomically quite profound in the interlobular vessels causes a more severe ischemia than that found in patients with chronic glomerulonephritis or arterial or arteriolar nephrosclerosis. This perhaps is the reason why the arterial tension is proportionately higher in chronic pyelonephritis lenta than in other chronic kidney diseases. The arteriolosclerosis found in chronic pyelonephritis lenta is probably a phenomenon secondary to the prolonged and severe hypertension (Goldblatt [19]). However, it also may represent the end result of an inflammatory arteriolitis similar to the deforming endarteritis found in the larger intrarenal vessels.

Arteriolonecrosis, as shown above, is obviously a terminal or preterminal occurrence because of the absence of significant reaction to either the necrosis or hemorrhage. It cannot be too strongly emphasized that careful search is frequently required to find these lesions, since they are often quite sparse. The quest into the etiology of this arteriolar lesion has been widespread, many different causes having been postulated, both separately and in combinations. It has been called inflammatory (Volhard and Fahr,[1] MacMahon [20]), toxic (Fahr [5]), and ischemic (Jores,[2] Löhlein,[3] Volhard [4]). Klemperer [17] believed that it was degenerative, and Fishberg [13] that it was traumatic due to the persistent extreme elevation of the diastolic arterial blood pressure producing acute arteriolar damage. We agree with Goldblatt and others that the necrosis is due to the action of a toxic "x"-substance found in uremia or pre-uremia on arterioles already damaged by arteriolosclerosis. The resulting hematuria and gross petechial hemorrhages unwarrantedly gave the disease the name "malignant" nephrosclerosis.

In most communications on the subject of "malignant" hypertension and "malignant" nephrosclerosis, the arteriolonecrosis with its consequent hemorrhages is regarded as the causative, characteristic lesion. However, since these lesions are quite irrelevant etiologically to the primary disease of the kidney, it would seem wiser to give up the obscure descriptive terminology of "malignant hypertension" and "malignant nephrosclerosis" in favor of more accurate etiologic nomenclature. In the vast majority of cases the diagnosis of chronic pyelonephritis lenta with superimposed acute pyelonephritis can be made. This tendency becomes especially important in those cases of unilateral renal disease with hypertension amenable to surgery.

As to the pathogenesis of pyelonephritis lenta, we can add little to prevailing theories. Whether the infection is a primary hematogenous one, an ascending one or, what is more likely, a combination of both, is still an intriguing problem. In two of our patients we found a history of gonorrhea; several were diabetic, and several had had pyelitis of pregnancy some years previously. These coincidences are too few to be interpretable. However, we are impressed by a certain similarity between chronic glomerulonephritis and pyelonephritis lenta. Both frequently exhibit obscure, often untraceable acute episodes, and both frequently have long latent periods during which the scarring proceeds inexorably to severe renal damage. Because of the principal involvement of the renal parenchyma, patients with chronic glomerulonephritis often show sudden renal failure. Since in pyelonephritis the principal involvement is interstitial, with secondary arterial changes, these patients present initially the syndrome of hypertension and then, with a superimposed insignificant acute pyelonephritis or sudden demand for increased renal function, proceed to a termination with uremia. Just what changes occur between the early acute lesions and the ultimate appearance of the final symptoms, we do not know.

The question might arise as to the reason for calling these kidney changes pyelonephritis, since the most significant changes are within the interstitial tissue and blood vessels. Perhaps chronic interstitial nephritis may be a more accurate term. However, this terminology was greatly misused during previous years and was commonly applied not only to those kidney changes designated now as nephrosclerosis of the arteriolar variety, but also to chronic glomerulonephritis, syphilitic nephritis, etc. Besides, in pyelonephritis there are always changes in the tubular apparatus, such as atrophy of tubules, regeneration of lining cells of tubules, and dilatation of certain tubules. Because of the changes in the pelvis, which are often though not invariably present, and because of the confused usage the name chronic interstitial nephritis has been put to, the terminology "chronic pyelonephritis" was retained. It was modified by the adjective "lenta" to differentiate this type of inflammation from the destructive variety, and to indicate the slow, insidious, progressive course of the diffuse disease.

Summary

Fifty autopsied cases of hypertension with uremia ("malignant hypertension") were studied and compared with a similar group of 50 cases of essential hypertension complicated by vascular accidents or heart failure. Analysis of the clinical features showed that the uremic series exhibited a lower average age, a greater degree of hypertension, constant anemia, frequent albuminuria and inconstant urinary findings. The kidneys were grossly smaller, and exhibited shallow, yellowish-pink cortical scars, and scars of the pelves. The heart was uniformly hypertrophied. Histologically, 43 of the 50 cases exhibited severe diffuse chronic pyelonephritis, three exhibited acute pyelonephritis, three a combination of slight to mod-

erate diffuse pyelonephritis with arteriosclerosis and arteriolosclerosis, and one only arteriosclerosis and arteriolar sclerosis. The arterial lesions are considered to be inflammatory rather than degenerative, and are called arteritis deformans. An ischemic mechanism of this type of hypertension is postulated. The rôle of arteriolonecrosis is discussed, and it is concluded, principally because of no or very little reaction to the necrotizing lesion, that it is a result rather than a cause of uremia. An acute exacerbation of the pyelonephritis was found in 50 per cent of the cases and was determined to be the common precipitating factor of uremia. Because of the evidence presented, it is suggested that the terms "malignant hypertension" and "malignant nephrosclerosis" are vague and not etiologic, and should therefore be discarded. Finally, it is further suggested that diffuse chronic pyelonephritis of this type be named pyelonephritis lenta, because of its insidious onset and course and so that it may be separated from the destructive variety of pyelonephritis.

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DIAGNOSTIC PROBLEMS OF RHEUMATIC FEVER AND THEIR IMPACT ON THE MANAGEMENT OF THE RHEUMATIC FEVER PATIENT *

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THE American Council on Rheumatic Fever, through its Committee on Community Rheumatic Fever Programs, has recently conducted a survey on a representative sampling of programs to get answers to some of the many questions related to the management and control of this complex and elusive disease.

To report to the cardiologists of the country on *one* aspect of the survey, namely, the common diagnostic problems encountered in rheumatic fever clinics and wards, and their implication for the management of patients or suspects, is not only a privilege but also almost an obligation. For it is to the cardiologist that the community and allied professional workers will look for guidance in the supervision and care of persons with present or past rheumatic fever or rheumatic heart disease.

His responsibility is threefold:

First, the cardiologist is, of course, called upon to help in the early detection and identification of children and young adults with rheumatic fever and rheumatic heart disease, or to give assurance that neither rheumatic infection nor cardiac disease is present.

Second, he has to be prepared for a full evaluation of the therapeutic, educational and social aspects of the individual case. He has to be ready and willing to make specific medical recommendations for a personalized program that will promote a suitable life adjustment for those handicapped by recurrent infection or by cardiac disease.[1]

When he has fulfilled these duties of a consultant, the cardiologist can no longer afford to leave to others the task of carrying out his recommendations with whatever resources may be available. In close coöperation with other professional workers, he will have to assume a *third* type of responsibility—leadership in the planning and organization of all the services and facilities that must be provided in a community or an area against the threat of an insidious, protracted and at times catastrophic disease such as rheumatic fever.

With this in mind, we may approach one of the diagnostic problems and its consequences. A fairly typical illustration of such problems is the following comparison of referral and verified diagnosis from community S.

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It deals with 275 consecutive admissions over a three year period to a rheumatic fever clinic in a city-rural area program.

It will be noted in table 1 that in 62 out of 275 referrals, patients were sent to the clinic without any statement as to findings, opinion or special questions from the referring physician. This omission deprives the consultant group of the chance to give due concern to the family physician's opinion or commitment when they interpret to the parents the clinic findings and recommendations.

However, in the first 100 consecutive admissions we find 35 referred without any diagnostic statements or explanation, in the following 175 cases only 27. This drop from 35 to 15 per cent was due to more effective contacts between practicing and consultant physicians. In many of the 175 cases a concise questionnaire card was sent to the family physician.

TABLE I

275 Consecutive Referrals Seen in a Rheumatic Fever Clinic within Three Years

	275 Admissions		First 100 Cases		Rest of 175 Cases	
Diagnosis *not* stated	62	22.6%	35	35%	27	15.4%
Statement made	213	77.4%	65	65%	148	84.6%

Referral and Verified Diagnoses

A comparison in 212 cases

Both diagnoses agree	40	19%
Diagnoses do not agree	34	16%
Referrals for evaluation	137	65%
No verified diagnosis available	1	
Total cases	212	100%

Among the 275 referrals, a statement that might be interpreted as a definite diagnosis was made in only 74 (or 27 per cent) of the cases. Forty referral diagnoses, or one-fifth of all, were confirmed in the clinic; in 34 cases, major disagreement with the attending physician's diagnosis resulted. One hundred thirty-seven cases were referred for evaluation.

For 212 cases, an overall comparison between the referring and verified diagnoses is shown in table 2. The tabulation presents the diagnoses of both groups as to the absence or presence of rheumatic infection, and separately as to absence or presence of cardiac disease. It became apparent from the case study that sometimes the question of rheumatic infection was paramount in the practitioner's mind. He then made no comment (in 83 of 212 cases) about the cardiac status. In other instances, detection of a murmur led to the referral, but no indication was given (in 66 of all cases) whether a careful history regarding the etiology of the murmur had been taken prior to the referral.

In some cases the referring physician's opinion could only be inferred, whereas the criteria and policy of the consultant group were clearly defined. For this reason, the referral statements, many of which could hardly be considered a formal diagnosis, were interpreted as generously as possible in terms of the verified diagnoses. The discrepancies as tabulated are, therefore, a minimum and might actually be higher.

Only three out of 19 referrals with a diagnosis of some stage of rheumatic fever were confirmed. (Adding the undiagnosed referrals, in the whole series of 275 cases, six were found with active rheumatic fever or chorea.) Only four cases of suspected or questionable rheumatic fever were confirmed by the consultants, whereas 73 such cases are listed among the referrals. This does not necessarily imply that suspected cases were overdiagnosed, because many of the 73 cases were obviously referred for the

TABLE II

Referral and Verified Diagnoses in 212 Cases Admitted to a Rheumatic Fever Clinic

Diagnosis of R F	Referral		Verified		Diagnosis of Cardiac Status	Referral		Verified	
Acute or low grade	6	19	3		R H D, acute	2		1	
					R H D, inactive	7	29	12	43
Stage undetermined	13		0		Congenital H D	22		31	
Pos. history	24	97	28	32	Possible H D	10		13	
Questionable hist.	73		4		Evaluation of H D	74		0	
NO history	30		174		No H D, NO murmur	13		80	152
					No H D, Mm. functional	1		72	
Not stated	66		3		Not stated	83		3	
Total cases	212		212			212		212	

legitimate, or rather, desirable purpose of evaluating a possible case of rheumatic fever. At any rate, the consultants were able, in about two-thirds of the 97 cases in which a positive or possible history of rheumatic fever led to the consultation, to remove any doubt as to the presence of this formidable disease. What this means, in terms of relief from anxiety for the family and restitution to a normal life for the child, hardly needs further discussion here.

The ratio of 31 congenital to 12 rheumatic organic cases illustrates the important and inseparable rôle of the rheumatic fever program in case-finding of congenital heart disease.

Finally, the table shows that in 152 (or almost 73 per cent) of 209 cases, the presence of heart disease could be ruled out. Almost half this number (47.4 per cent) had a physiologic murmur.

A few of the referral statements may be quoted, because they indicate the need for providing more effective postgraduate education in rheumatic fever. Referral statements frequently ask for "evaluation for cardiac murmur," without any attempt to describe location, type or behavior of the murmur. In other instances, only one symptom, such as "chest pain," or unexplained opinions like "rheumatic condition," "mild rheumatic manifestations," "active atypical rheumatic fever," were offered.

Here is the place where one of the cardiologist's "third responsibilities" comes in: When a rheumatic fever program is organized or maintained, and arrangements for a referral system are made, much thought should be given to referral forms. This is more than an administrative detail.[2] Nothing seems so educational in diagnostic work as to be committed to a diagnosis.

If we want to improve case-finding and also "delabeling" of so-called cardiac children, if we want to improve the diagnostic skill required from *all* physicians, it will be necessary to state diagnostic criteria and to determine an acceptable way of classifying cardiac diagnoses by cardiologist, family physician and school physician alike. The classification of heart disease, in accordance with the Nomenclature [3] in which the New York Heart Association pioneered more than 20 years ago, and which has been adopted by the American Heart Association, may require some modification in view of recent developments and changing concepts in cardiology. Such changes are being carefully studied. But even as it stands, the Nomenclature gives all physicians a chance to use a comparable classification of causes, structure and functions, and a broad grouping as to permissible and desirable physical activities. Unfortunately, it is not used so widely as it could be. The only group which insists on its nationwide use is not a medical group, but the Vocational Rehabilitation Service.

These are common diagnostic problems encountered in rheumatic fever programs. Table 3 deals with the verified diagnoses of a rheumatic fever program in community D. The series is not only one of the largest (over 3,000 cases) started in recent years, but it is based on published and very precise diagnostic criteria.[4] It comes from one of the really outstanding rheumatic fever clinics visited during the survey. You will note that in 6.6 per cent, a diagnosis of active rheumatic state could be ascertained. In about one out of 10 cases the problem of definite or suspected rheumatic activity arose.

The most relevant result for which this table is being presented is the fact that in two out of five cases (or exactly 41 per cent of 360 cases), this highly experienced group devoted to clinical research in rheumatic fever and working in a well equipped institution was unable to advance its diagnosis beyond the suspicion of activity until a decision could be made after prolonged observation.

The right side of the table indicates that 36 per cent of 580 patients with organic heart disease had congenital or probably congenital defects.

Thirty to 40 per cent of congenital heart disease among all organic heart disease is being reported from most rheumatic fever clinics.

On the whole, the table is highly reminiscent of the smaller series of verified diagnoses on the first table. In over two-thirds of all admissions, heart disease could be definitely ruled out. In 20 per cent of 703 diagnoses of heart disease, the decision as to presence or absence of organic defects had to be deferred.

This seems to be the limit of diagnostic acumen among highly trained and judicious cardiologists. In another rheumatic fever program covering

TABLE III

Diagnoses of 3,230 Verified Cases Seen in a Rheumatic Fever Clinic (Within Four Years)

A.

Rheumatic Infection	No.	%	Cardiac Status	No.	%
Active	213	6.6	R H D, organ. 355; poss. 123; pot. 378	856	26.5
Questionable	148	4.6	Congen. organ. 190; H D poss. 20	210	6.5
Pos. or poss. hist.	578	88.8	H D other or type unknown	15	.4
No history of R F	2291		*No H D*, no murmur 448; with murmur 1579; Mm. not stated 132	2149	66.6
Total cases	3230	100.0	Total cases	3230	100.0

B.

Rheumatic Infection	No.	%	Organic Heart Dis.	No.	%
Definitive active	213	58.9	Rheumatic	355	61.2
Questionable active	148	41.1	Congenital	210	36.2
			Other or type unknown	15	2.6
Total	361	100.0	Total	580	100.0

a state, the majority of cases are examined, or at least evaluated, by the staff of a medical school. Here the registry figures were as follows: during the eight years following 1940, of 1,205 diagnoses, 21 per cent had to be deferred; and in 1949, of 1,005 examinations, 21.1 per cent (though very accurate criteria for the diagnosis of valvular and possible heart disease had been published from this clinic).[8]

Figures like these could be repeated in many communities throughout the United States. During the past six years, an average of 5,000 to 6,500 visits per year was made to the clinics of the Cardiac Consultation Service

of the New York City Department of Health.[6] Even though the Service utilizes qualified cardiologists for consultation, in more than one-fifth of the cases (1,232 cases out of 6,032 admissions in 1948) it was not possible to determine in one visit whether organic heart disease was present.[7] In such instances the patient is followed through periodic reëxaminations, but we have tried to avoid carrying children with the diagnosis of so-called [8] "possible heart disease" for more than two years without deciding whether heart disease is present. It often takes a long time and persistent interpretation and follow-up to remove from the mind of parent, teacher and child all apprehension caused by having been labeled, even though tentatively, a "cardiac."

As a matter of general policy we have felt that it is better to err on the side of optimism in cases that remained doubtful after several reëxaminations. If a diagnostic error cannot be avoided in such cases, less harm will be done in judging a child with equivocal evidence of heart disease as "non-cardiac."

TABLE IV

Discharges from a Teaching Hospital
(Pediatric Wards) 1940–1949

Active R F or Active R H D	81 cases
Suspected Rheumatic Activity	23 cases
Inactive Rheumatic Heart Disease	8 cases
Chorea, Active	9 cases
Total Cases of Rheum. State	121 cases

We have found that, because of murmurs that bore all the characteristics of a physiologic murmur of no consequence, children had been excluded from all gymnastic activities or even confined to bed for long periods of time. Far from being a waste of effort, the need for consultation services is accentuated by the fact that the classification "non-cardiac" could be definitely established in a group of more than one-third of the children referred to the Health Department clinics as suspected of or having cardiac disease.[9]

It might be argued that in many of the cases in which a diagnosis with regard to rheumatic activity had to be deferred, a transfer from the clinic to the wards might lead to unraveling our diagnostic dilemma. The following data from the pediatric wards of another University Hospital (Community C), this time at the West Coast (table 4), are not encouraging to our hopes that we may break out of the limits in diagnosing rheumatic fever without the benefit of new diagnostic methods or observations. It is true that the reputation of this hospital attracted not only severe cases but also many which were difficult to diagnose. At any rate, the table illustrates the fact that of 112 patients referred because of rheumatic fever during the past 10 years, 23 were discharged with a diagnosis of suspected rheumatic activity. A staff of experienced and meticulous observers in a teaching hospital were unable to rule out or to confirm the presence of activity in 20 per cent of patients in whom rheumatic fever posed a problem. About

two-thirds of the cases had been observed on the pediatric ward for a period of between 10 days and two months.

It has been possible to touch but briefly and in a very general way upon some important facets of diagnostic problems. The importance of rheumatic fever is based not only on results in morbidity and mortality figures for evident cases. It is of public health interest because of the complex problems involved in precise diagnosis of smoldering and subsiding infections, or in determinations of the presence or absence of organic heart disease. An unbiased diagnostic approach by both the referring physician and the clinician is essential for the cardiac patient and for the non-cardiac individual erroneously labeled rheumatic or cardiac. Otherwise, cases are missed or —what can, no doubt, be quite as serious—individuals are needlessly subjected to medical care and restrictive measures, with grave psychologic and social consequences.

Only close coöperation between clinics, hospitals, practicing physicians and an integrating rheumatic fever community program can deal effectively with this long-term protean disease. Such a program remains incomplete and in many ways ineffective unless the physicians make full use of nursing, social and educational services and of vocational guidance to reduce the serious effects of the rheumatic state and of frequently unavoidable delays in diagnostic clarification.

From the viewpoint of disease control, rheumatic fever holds a position between the infectious diseases and chronic illness. Its relation to streptococcus infections points to the application of well-tried public health measures in our attempt to eradicate this disease—namely, chemoprophylaxis, the use of case registers, health education, development of adequate facilities for the indigent and medically indigent families, etc.

Its prolonged and at times disabling character clearly places rheumatic fever among the chronic diseases. We need, therefore, a concerted effort by public health and community workers, together with the family physicians and clinicians. Early detection of this illusive disease must be accomplished by attrition rather than by mass procedures. It has to be done by clinical processes. It requires a system of periodic examinations by physicians now generally used in conjunction with the school health services but undeveloped for young adults. Dr. Bland's and Dr. Jones's unique experience has just impressed us with the importance of good supervision and care of rheumatic fever patients in the third decade of life and beyond.[9] The natural history of rheumatic fever necessitates continuity of care over long periods of time, with a knowledge of all the factors that mold the patient's life.

The cardiologist whose decisions form the basis of further educational and vocational planning cannot limit his interest to valvular defects and to the obviously handicapped. It is part of his responsibility to develop in the community an understanding of rheumatic fever as a long-term, repetitive and often economically catastrophic disease. It is equally essential that he

use his authority to spread the knowledge that the majority of rheumatic children who reach adolescence are by no means seriously handicapped. Experience with the rheumatic fever programs has shown that communities may be alerted to the needs of obviously handicapped cardiac children but fail to provide a reasonable amount of supervision for questionable cases, or for individuals with a history of rheumatic fever who show no evidence of cardiac involvement.

In these latter cases the rôle of the consultant as an educator of the community, of the family physician and of the parents is evident. Parents, nurses and other community workers are confused by the discrepancies of medical opinions resulting from lack of uniform criteria and standards of adequate care, particularly from conflicting recommendations for physical activities. In this area lies one of the urgent and most delicate tasks of the consultant. He is often forced to oppose the unwarranted restrictions which may have been recommended as a so-called safety measure, or which are based on an erroneous application of principles valid only for the management of cardiovascular disease in middle aged and older patients.

We have thus returned to the cardiologist's *third* responsibility: Preventive measures and the judicious management of questionable cases will require just as much of his attention as the care of advanced cases. To correct an erroneous diagnosis of heart disease based on an adventitious murmur and to insist on a normal and active life will be as important to him as to make a differential diagnosis of a rare congenital cardiac anomaly. He cannot confine his interest to the structure and function of the heart but must consider the social structure of the rheumatic family and of the community in which the patients live.

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SOFT TISSUE CALCIFICATION, WITH SPECIAL REFERENCE TO ITS OCCURRENCE IN THE "COLLAGEN DISEASES" *

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INTRODUCTION

CALCIFICATION is a process which results in the accumulation of lime salts in a tissue in amounts which are demonstrable on microscopic, roentgenographic and often on naked-eye examination. Normally this process involves only bones and teeth, and when any other tissue is the site of calcium deposition, pathologic calcification, or calcinosis, is said to exist. Although there has been much investigation of this subject, the exact mechanism is not known whereby demonstrable aggregates of the carbonate and phosphate of calcium are produced from invisible components present in blood and tissue fluid.

Normally the amount of calcium and phosphorus in the blood serum is maintained within a narrow limit. This limit is the result of a dynamic equilibrium [1, 15] dependent upon the absorption of these materials from the gut, their resorption from or deposition in the bony storehouse, and their excretion by the kidney and bowel. Vitamin D and parathyroid hormone exert their influence upon blood concentrations by affecting one or the other of these basic processes. The agents which maintain normal blood values for calcium and phosphorus will be referred to later as factors distant from the site of calcification which regulate calcium metabolism.

The equilibrium level set by the regulating factors is such that at a normal carbon dioxide tension the blood serum and interstitial fluid are essentially saturated with calcium and phosphate ions. If an increase of calcium ions occurs without a compensatory decrease of phosphate ions, or the reverse, precipitation of insoluble calcium phosphate occurs. In other words, at a given carbon dioxide tension, insoluble salt is precipitated when the product of calcium and phosphate ions exceeds a certain limit. If the carbon dioxide tension decreases, thereby causing the medium to become more alkaline, fewer calcium and phosphate ions can be held in solution and calcium phosphate is again precipitated.

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Certain pathologic states may cause an increase of calcium or phosphate ions or both in the blood serum and interstitial fluid. When the increase is great enough to exceed the solubility product of calcium and phosphate ions, calcium phosphate is precipitated in normal tissue. Usually the salt is precipitated in tissues such as lung, stomach and kidney [23] where the carbon dioxide tension is normally low, but precipitation may occur anywhere. Calcification of normal tissue may be found in hyperparathyroidism vitamin D intoxication, destructive bone diseases and pseudohypoparathyroidism.[1, 23]

A more common type of calcification occurs in the presence of normal amounts of calcium and phosphate ions in blood serum and interstitial fluid. The best example is normal calcification of bone. It is thought that osteoid tissue contains enzymes that release phosphate ions from suitable substances.[1, 19] The local increase of phosphate ions raises the product of calcium ions and phosphate ions beyond the point of solubility, and the precipitation of calcium phosphate occurs. There is some evidence that injured tissue may serve as a substrate for a phosphorus releasing enzyme,[12, 14, 20, 31] so that calcification in this instance may occur through a similar mechanism. In addition, injured tissue may develop a lowered carbon dioxide tension, so that fewer calcium and phosphate ions can be held in solution.

It is recognized that the above discussion does not include all the theories of calcification. In the interest of brevity, the more controversial material has been omitted.

When calcification occurs, the salt deposited has a definite chemical and physical structure. There is formed a crystalline substance belonging to a group of naturally occurring minerals called apatites.[1, 9] A general formula for this group is $nCa_3(PO_4)_2 \cdot CaX_2$. The mineral deposited in bone approximates dahlite, an apatite which has a formula $2Ca_3(PO_4)_2 \cdot CaCO_3$. Roentgen-ray diffraction studies [9] and chemical analyses indicate that the deposits of pathologic and normal calcification have the same physical and chemical structure.[2, 4, 7, 41, 42, 47, 56, 62, 70, 71, 72, 73] The similarity between normal and pathologic calcium deposits is expected, since they are in equilibrium with each other through the blood and interstitial fluid.[1]

Classification

Whatever the exact mechanism of pathologic calcification may be, it is quite clear that two abnormal states result in a deposition of lime salts in soft tissue: I. Tissue injury may serve as a stimulus to calcification. II. Metabolic abnormalities resulting in an increased serum concentration of calcium, phosphorus or both may result in pathologic deposits.

Bearing in mind these two abnormal states, a working classification of calcinosis can be formulated:

A. Calcification due to tissue injury

1. Calcification associated usually with localized injury and a known injurious agent—the so-called dystrophic calcification
   A. Mechanical or physical trauma
   B. New growths
      1. Benign
      2. Malignant
   C. Parasitic infestation
   D. Foreign body
   E. Circulatory disorders
      1. Venous
      2. Arterial
   F. Infectious processes
   G. Congenital defects

2. Calcification associated with widespread tissue injury of unknown origin
   A. Scleroderma and/or Raynaud's syndrome
   B. Dermatomyositis
   C. Lupus erythematosus
   D. Rheumatoid arthritis
   E. Acrodermatitis atrophicans chronica
   F. Mixed collagen disease

B. Calcification due to abnormality of calcium and/or phosphorus regulation remote from the site of the deposit. Abnormal levels of serum calcium and/or serum phosphorus obtain in this group

1. Hyperparathyroidism
2. Renal insufficiency
3. Vitamin D intoxication
4. Destructive bone disease
   A. Metastatic carcinoma
   B. Osteomyelitis
   C. Leukemia
   D. Multiple myeloma
   E. Paget's disease of bone
5. Pseudohyperparathyroidism

At times both tissue injury and remote metabolic abnormalities operate in pathologic calcification, but in such instances one factor is usually so dominant that the above classification is still functional. In this scheme, group B includes the so-called metastatic calcifications as well as those due to hormonal abnormalities, because the basic disturbance of serum calcium and phosphorus levels is present in both groups so that essentially the same fundamental cause of calcification is represented.

Calcinosis Circumscripta and Calcinosis Universalis

Calcinosis circumscripta and calcinosis universalis are terms commonly used in the literature. These types of pathologic calcification imply the deposition of calcium salts in several, often symmetrical areas of the skin and subcutaneous tissue. When deposits are few, and limited in large part to the hands and feet and the vicinity of the large joints, the condition is referred to as calcinosis circumscripta. When generalized calcification involves subcutaneous tissue, fibrous tissue of muscle and sometimes tendon, the condition is called calcinosis universalis. Such terms are purely descriptive and, as such, should carry no diagnostic connotation, for the same type of soft tissue calcification may occur in hyperparathyroidism, vitamin D intoxication, dermatomyositis, renal insufficiency and carcinomatosis with metastases to bone. The descriptive adjectives circumscripta and universalis, though widely used, are equivocal terms. It is impossible to know where circumscript calcinosis ends and universal calcinosis begins in a spectrum of disease states associated with all degrees of calcification from two or three deposits to almost complete encasement in a shell of lime.

Much of the confusion and mystery surrounding the use of the terms calcinosis circumscripta and calcinosis universalis stems from the practice of regarding calcification as a primary process. If the situation at hand is closely examined, it seems that there will always be found a primary disease responsible for the calcification. Therefore, the terms calcinosis circumscripta and calcinosis universalis should be used only in conjunction with a primary diagnosis. For instance, that disorder which formerly was called calcinosis circumscripta should be referred to as scleroderma with circumscript calcification, or Raynaud's syndrome with circumscript calcification. Calcinosis universalis should, on etiologic grounds, be called dermatomyositis with universal calcification, or sclerodermatomyositis with universal calcification. When calcinosis occurs in renal failure,[8] it should be referred to as renal failure with universal calcification, or renal failure with circumscript calcification. In this way attention will be focused upon the primary diagnosis rather than upon the calcium deposits. Diagnostic errors and confusion will be avoided. If a patient such as the one reported as an example of calcinosis universalis by Lutz [21] in 1941 is examined more closely as to etiology, one finds a serum calcium level of 24 mg. per cent and a serum phosphorus of 2.9 mg. per cent. These metabolic changes most likely represent an instance of hyperparathyroidism with calcification; hence, the primary disease is obscured by the "diagnosis" of a secondary complication, calcinosis universalis. Renal failure, dermatomyositis, scleroderma and pseudohypoparathyroidism [21] are sometimes overlooked in the enthusiasm generated by the abnormal calcium deposits and the "diagnosis" of calcinosis.

Twelve cases of so-called calcinosis circumscripta or calcinosis universalis were found in the University Hospital file. All 12 cases were analyzed

to determine the primary disease process. Two of them will be presented in detail and 10 in abbreviated form.

Case Reports

Case 1. A 19 year old white female was first seen at the University Hospital in March, 1948. In the winter of 1946 and 1947 she had suffered a moderately severe frostbite of the fingers. By the fall of 1947 she noticed pallor of the fingers associated with emotional tension or exposure to cold. A reticulated, erythematous eruption involved the extremities, face and trunk in February, 1948. A month later, dystrophic changes of several fingernails and edema of the face, hands and one ankle appeared. She lost about 20 pounds and became tired and weak. Bending over was particularly difficult. Treatment consisting of tar and soda baths, narcotics, pyribenzamine, Thephorin and a few injections of Etamon was of no avail.

Physical examination revealed a reticulated macular eruption of the extremities, trunk and face, cyanotic nailbeds, erythema of the distal third of the fingers and toes, and a separation of most of the fingernails from the distal third of the nailbed. There was edema of the face, the ocular fundi, the hands, one ankle and one knee. The mucous membranes of the nose were boggy, and there was a nasal quality to the voice. The muscles seemed to be harder than normal. There were persistent fever and tachycardia.

Laboratory findings were as follows: Hemoglobin, 83 per cent; white blood count, from 6,250 to 9,450 with normal differential values; normal urea clearance; nonprotein nitrogen, 21.5 mg. per cent; blood urea nitrogen, 6.9 mg. per cent; negative Kahn reaction; negative urinalysis. A skin biopsy from the face presented a non-

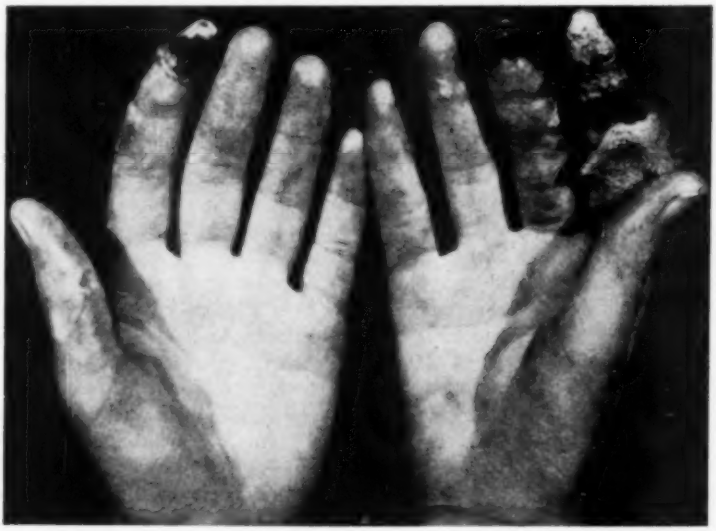

Fig. 1. (Case 1.) Hands, showing sclerodermatous skin, contractures, calcium deposits and gangrenous fingers.

FIG. 2. (Case 1.) Roentgenograms of the hands to show the amount of calcification.

specific inflammatory reaction. A muscle biopsy showed perivascular lymphocytic infiltration.

From March, 1948, to April, 1949, she was followed as an out-patient. Most of this time she was taking potassium para-aminobenzoate and multivitamin capsules. On several occasions there was fever as high as 103° F. At times it was thought the fever represented a reaction to the para-aminobenzoic acid, so that much of the time the drug was used in inadequate doses. It was entirely possible that the fever and exacerbation of symptoms represented only variations of her disease. Calcium deposits were first noticed about the buttocks in February, 1949. Since the patient failed to improve, she sought medical attention elsewhere.

Between April, 1949, and readmission in October, 1949, she was seen by many physicians and received many forms of treatment, including penicillin, aureomycin, antihistaminics, vitamins, calcium injections, bistrimate, male hormone and Priscoline. Nothing arrested the progression of the disease. In May the right middle finger became gangrenous. In August the left index finger showed similar changes. Several calcium deposits about the elbows, buttocks and behind the knees formed ulcers and drained for extended periods. There was an additional 15 pound weight loss, and the menses, which had begun at age 16 and had been associated with a scanty flow every six to seven weeks, ceased altogether.

A report from the Mayo Clinic, where she was seen in June, 1949, was of interest. At that time there were cyanosis of both hands, one gangrenous finger, and the shoulder muscles were atrophic. Calcium deposits about the fingers and elbows were noted. Roentgen-ray examination of the chest and esophagus was negative. Other laboratory findings were: Serum calcium, 9.0 mg. per cent; phosphorus, 3.6 mg. per cent; 24-hour urinary 17-ketosteroid excretion, 2.0 mg.; blood urea nitrogen, 14 mg.

per cent; hemoglobin, 9.3 gm.; sedimentation rate, 124 mm. per hour Westergren; normal basal metabolic rate; Paunz test for amyloid negative. The diagnosis made was sclerodermatomyositis with Raynaud's phenomenon and calcinosis.

Physical examination in October, 1949, revealed a short girl (4′ 10″), weighing 100 pounds, 35 pounds less than her weight at the onset of her illness. The skin of the face, neck and backs of the hands was thick and "bound down" to the underlying structures. There were a seborrheic scale on the scalp, face and trunk and some bluish mottling of the extremities. The breasts were poorly developed; the axillary

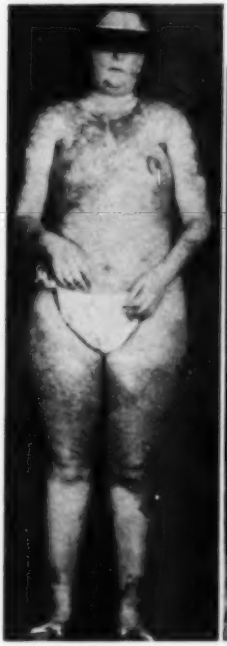

FIG. 3.

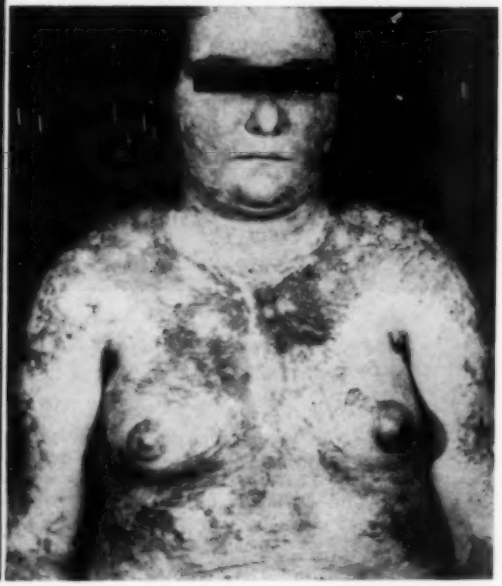

FIG. 4.

FIG. 3. (Case 2.) This picture shows the general body topography, the contractures of the arms and the extent of the poikiloderma. Picture taken in 1950.
FIG. 4. (Case 2.) Head and thorax, showing the facies and the poikiloderma.

and pubic hair was scanty. Massive calcium deposits were present on the posterior aspect of the thighs and buttocks, with smaller deposits about the arms, elbows, hands and knees. The tips of the first and second fingers of the right hand and the first finger of the left hand were gangrenous. The hands were bluish-red. About many of the calcium deposits was inflammation, and the deposits about the right knee, right buttock, anterior aspect of the left knee and both elbows had produced draining, ulcerated areas. There was muscle atrophy of the hands and shoulder girdle. Motion of the hands and elbows was restricted, and there was beginning flexion contracture of the right knee. A persistent tachycardia and low-grade fever were present.

Laboratory findings were: serum calcium, 8.7 mg. per cent, 10.2 mg. per cent and 9.1 mg. per cent; serum phosphorus, 4.2 mg. per cent and 3.9 mg. per cent; alkaline phosphatase, 3.2 mg. per cent; serum cholesterol, 141 mg. per cent; total serum protein, 8.6 gm. per cent; albumin, 3.7 gm. per cent; globulin, 4.9 gm. per cent. AG ratio, .76. Electrophoretic examination indicated a protein pattern as follows:

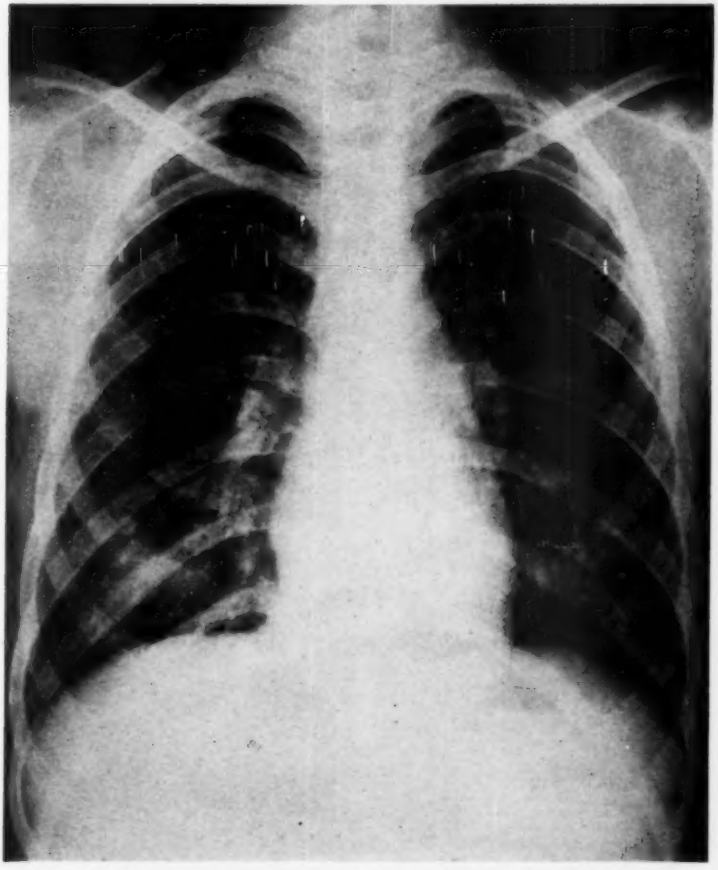

FIG. 5. (Case 2.) Roentgenogram showing sparsity of calcium deposits in 1941.

total protein, 7.7 gm. per cent; albumin, 2.34 gm. per cent; alpha 1 globulin, 0.48 gm. per cent; alpha 2 globulin, 1.14 gm. per cent; beta globulin, 0.90 gm. per cent; gamma globulin, 2.08 gm. per cent. Fibrinogen, 0.73 gm. per cent. AG ratio, 0.51. Carbon dioxide combining power, 50 vol. per cent. Basal metabolic rate, minus 4. Blood urea nitrogen, 9.27 mg. per cent, 7.0 mg. per cent, and 6.0 mg. per cent. Uric

acid, 6.6 mg. per cent and 5.7 mg. per cent. Fasting blood sugar, 62 mg. per cent. Non-protein nitrogen, 21.5 mg. per cent. Urine creatinine, 0.52 gm. per 24 hours. Urine creatine, 0.49 gm. per 24 hours. Sedimentation rate, 55 mm. per hour. Total serum bilirubin, 0.34 mg. per cent. Free (1 min.), .08 mg. per cent. Free (30 min.),

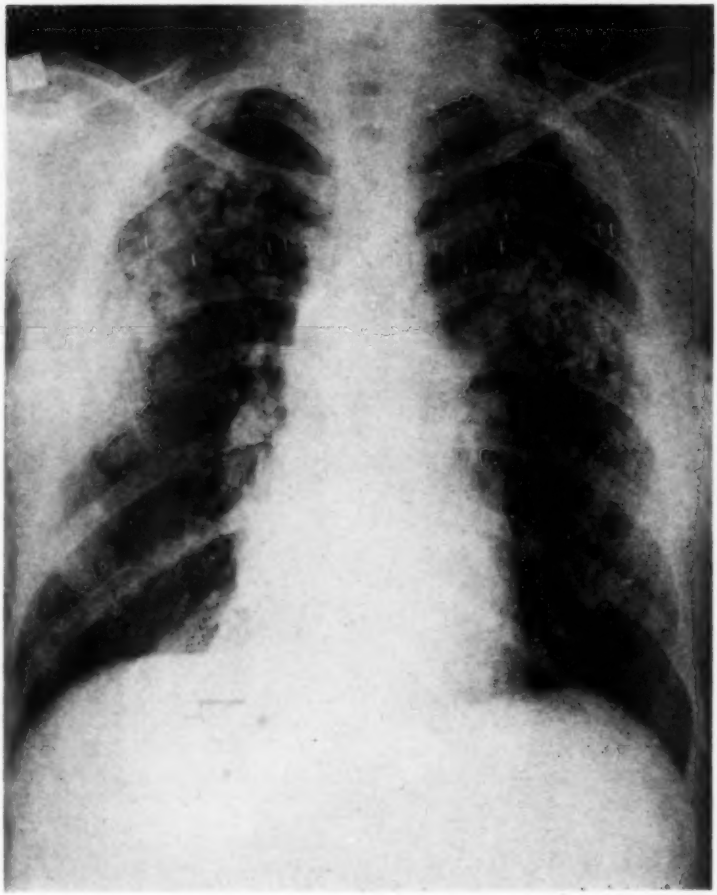

FIG. 6. (Case 2.) Roentgenogram showing striking increase of calcium deposits in 1950.

0.12 mg. per cent. Combined, 0.22 mg. per cent. Urine urobilinogen, 4.1. Ehrlich units. Total cholesterol, 149 mg. per cent. Free cholesterol, 46 mg. per cent. Cholesterol ester, 103 mg. per cent. Per cent ester, 69. Thymol turbidity, 15.0 units. Cephalin flocculation, 24 hours, 3 plus; 48 hours, 4 plus. Gamma globulin, 34.4 units. Serum bromsulfalein retention normal. Urinalysis negative except an occasional

white blood cell and 1 plus to 3 plus reducing substance while on para-aminobenzoic acid. Hemogram as follows: hemoglobin, 10.5 to 13.6 gm.; red blood count, 3.63 to 5.2 million. White blood count, 5,950 to 18,250; polymorphonuclear neutrophiles, 47 to 63 per cent. Lymphocytes, 26 to 50 per cent. Monocytes, 2 to 10 per cent.

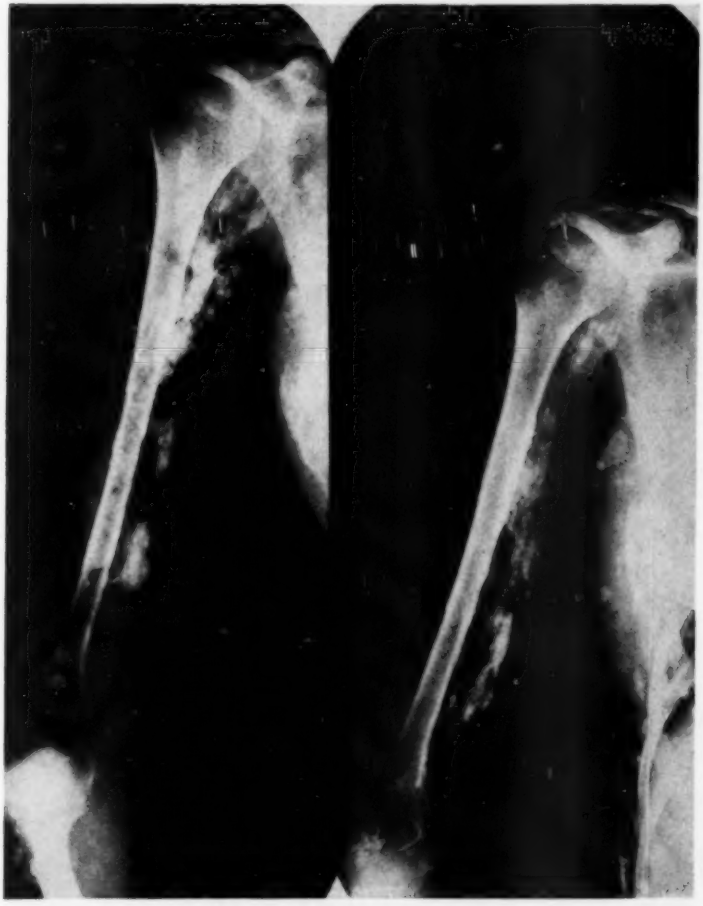

FIG. 7. (Case 2.) Calcification of the soft tissues of the arms.

Eosinophils, 1 to 7 per cent. Sulkowitch's test for urinary calcium, normal. Electrocardiogram normal except for tachycardia. Estrogen excretion, 4 rat units per 24 hours; 17-ketosteroid, 3.5 mg. per 24 hours.

Roentgen-ray examination showed slight osteoporosis about the elbows and wrists.

There was no calcinosis about the skull or face. Roentgenogram of the chest was negative. There was widespread calcification of soft tissue of the arms, legs, forearms, thighs, buttocks, pelvis, feet and hands. Skin biopsies showed chronic inflammatory changes. Focal myositis was evident on muscle biopsy. In the fat and

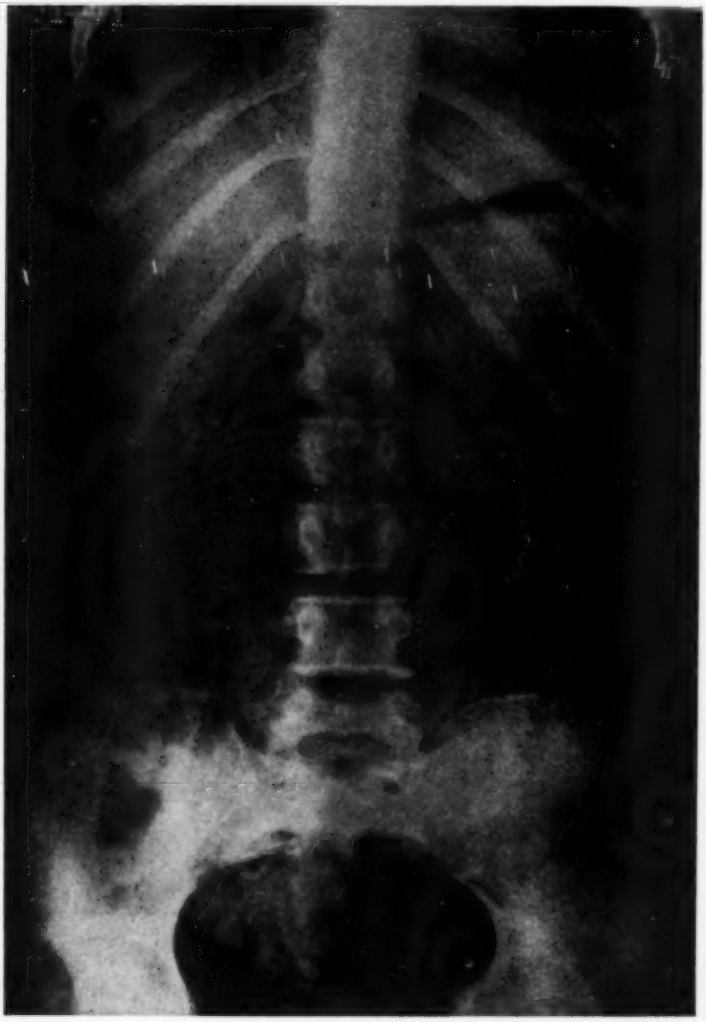

FIG. 8. (Case 2.) Minimal amounts of calcium in the abdominal and lower chest walls in 1941.

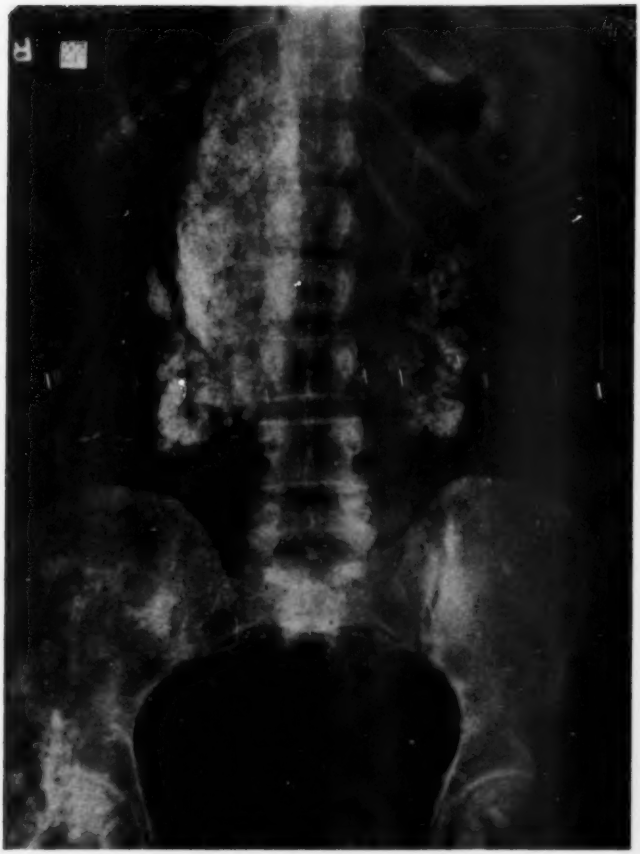

FIG. 9. (Case 2.) Increase of calcium deposition in the abdominal wall, in the pelvis and in the paravertebral muscles. Roentgenogram taken in 1950.

subcutaneous connective tissue occurred calcium deposits with chronic inflammatory change about these collections of lime salt.

While in the hospital the patient continued to have febrile episodes and the tachycardia persisted. Several nodules of calcium were extruded spontaneously. The calcium was surgically removed over the left knee, and a graft to the site healed readily. Other ulcerated areas filled in partially. A new area on the left buttock broke down and extruded calcareous matter. Penicillin had no effect on the fever. The patient received Priscoline, 50 mg. four times a day; vitamin C, 1.0 gm. per day; multivitamins; a 400 mg. calcium diet, appropriate local therapy and 14 gm. of potassium salt of para-aminobenzoic acid per day. She was discharged, to be followed in the out-patient clinic.

During 1950, three return visits indicated increased strength, continued healing of the ulcers, weight gain and healing by demarcation of the gangrenous fingers. More scale became apparent on the skin of the scalp and extremities. The scleroderma-tous skin became less hard and more pliable. There was less evidence of inflammation about the calcium deposits, though some continued to be extruded. Temperature remained normal for the most part, but with an occasional elevation to 100° F.

The final diagnosis was sclerodermatomyositis with Raynaud's phenomenon and universal calcinosis.

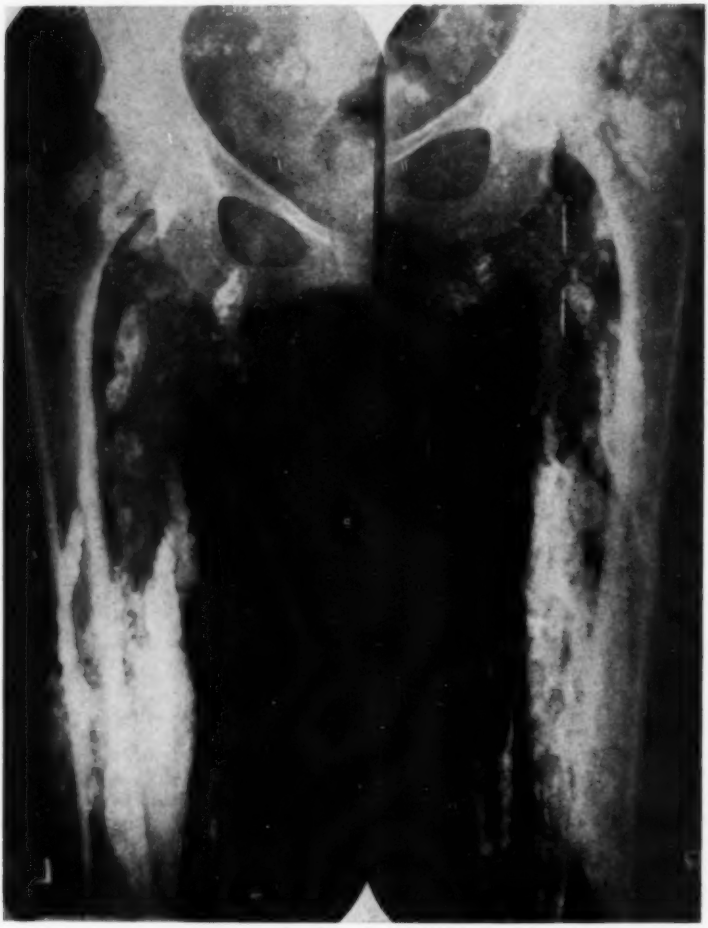

FIG. 10. (Case 2.) Extensive soft tissue calcification of the thighs.

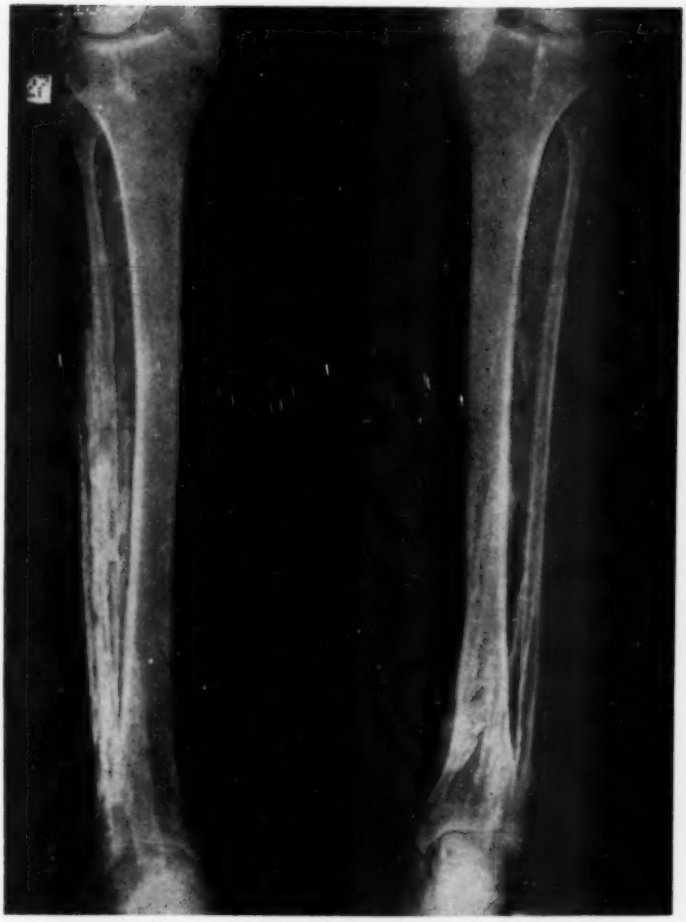

FIG. 11. (Case 2.) Calcium deposits in the soft tissues of the legs.

Comment: The primary disease was present for over a year before calcification became clinically evident. At no time were calcium or phosphorus values abnormal. It seemed most likely this represented deposition of calcium salts in diseased tissue rather than any disturbance of calcium regulation remote from the area of deposition. Follow-up was not long enough to determine the extent of benefit derived from para-aminobenzoic acid therapy.

Case 2. This 21 year old woman was followed in the Dermatology Department for 10 years. She presented a typical example of poikilodermatomyositis with cal-

cinosis universalis. There was no evidence of a primary disturbance of calcium metabolism.

Case 3. This 17 year old white girl was an example of widespread calcium deposition secondary to severe dermatomyositis. Serum calcium and phosphorus values were normal.

Case 4. Universal calcification developed in this 10 year old boy, whose primary disease was dermatomyositis.

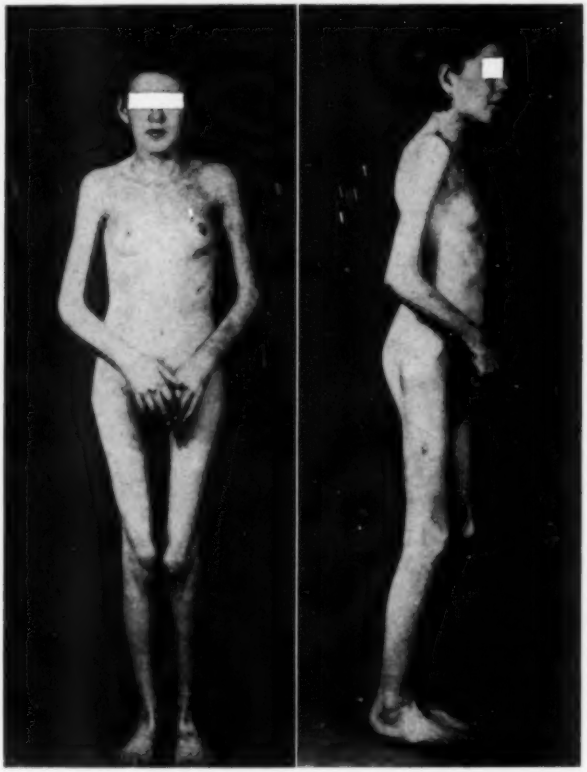

FIG. 12. (Case 7.) Showing muscle atrophy, contractures and poikiloderma.

Case 5. This case was an excellent example of the widespread calcification of connective tissue, tendon, artery and muscle that may develop in the course of severe dermatomyositis. There was no evidence of a disturbance of calcium metabolism remote from the site of the injured, calcified tissue.

Case 6. Extensive calcium deposits were found in this three and one-half year old girl. An illness highly suggestive of dermatomyositis occurred at two years of age.

Case 7. The primary disease affecting this 14 year old girl was dermatomyositis. Extensive tissue damage resulted in calcinosis universalis. Serum phosphorus and calcium levels were normal. An infection of the gastrointestinal tract proved fatal.

Case 8. There were features of both scleroderma and dermatomyositis in this patient's disease. The calcium deposits were irregularly distributed, so that it was difficult to classify them either as calcinosis universalis or calcinosis circumscripta.

Case 9. This 63 year old man had dermatomyositis of five weeks' duration. Biopsy of biceps muscle indicated the presence of calcium.

Case 10. A 56 year old married white female was seen in the University Hospital in 1949. Six years prior to admission she had noted frequent swelling of the hands and feet, followed one year later by tingling of the feet and blanching and pain

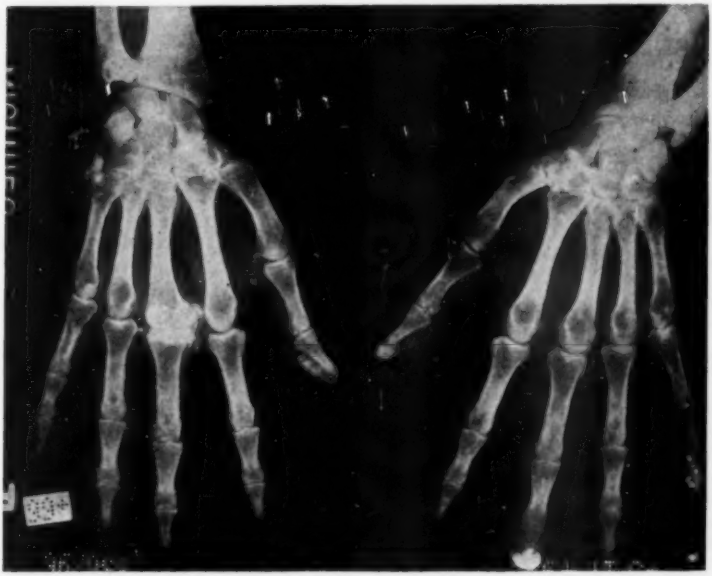

FIG. 13. (Case 10.) Circumscript calcinosis in scleroderma.

of the distal portions of the fingers upon exposure to cold. Four years before hospitalization a pruritic, macular rash appeared on the face. The patient was placed on thyroid, 1 to 4 gr. daily. About three months after thyroid therapy was begun, or about three years before the patient came to University Hospital, hard nodules were noted on the tips of the fingers. Soon thereafter these nodules appeared about the middle phalanges of the fingers, about the right knee and on the dorsum of the right foot. The skin about the face, upper trunk, upper extremities and lower extremities had become hard and stiff, and the patient felt lame and stiff "all over." Since the onset of the illness in 1943 there had been a 25 pound weight loss.

She had had an appendectomy, a tonsillectomy and three thyroidectomies done sometime in the 1920's. She had been pregnant eight times and had delivered two

normal children. Induced abortions accounted for the six terminated pregnancies. General health had been good until the onset of the present illness.

Physical examination revealed scleroderma involving the face, neck and upper trunk and the distal portions of the extremities. The hands were cold and moist. There were calcific nodules on the fingers, about the right knee, on the right foot and over the sternum. There were tapering and reduction in length of the terminal phalanges.

The laboratory findings were as follows: hemoglobin, 13.5 gm. per cent. Normal differential and total white cell count. Normal urinalysis. Normal urea clearance. Non-protein nitrogen, 33 mg. per cent. Uric acid, 4.9 mg. per cent. Total serum protein, 7.9 gm. per cent. Albumin, 4.3 gm. per cent. Globulin, 3.6 gm. per cent. Serum calcium, 9.4 to 7.8 mg. per cent. Serum phosphorus, 3.7 to 4.2 mg. per cent. The blood Kahn reaction was negative. A Sulkowitch test revealed normal amounts of calcium in the urine.

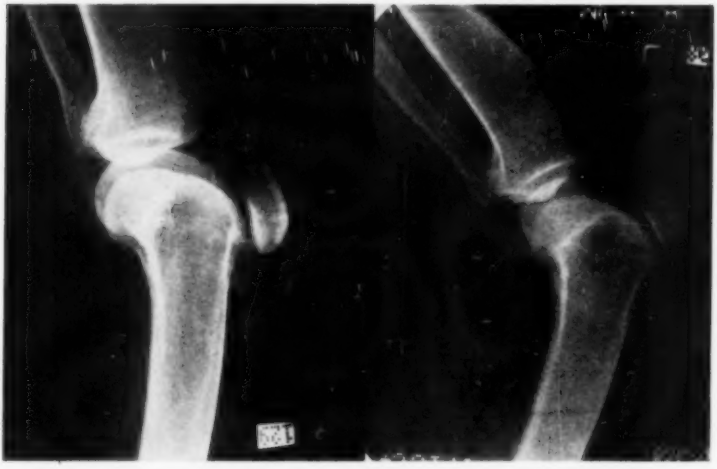

FIG. 14. (Case 10.) Calcium deposits about a knee in scleroderma.

The roentgenogram was reported as showing generalized osteoporosis, calcification of the pelvic lymph nodes and vessels, spontaneous amputation of the tips of the terminal phalanges, and calcium deposits in the soft tissues about the right knee and both hands.

Biopsy of skin and subcutaneous tissue from the right knee revealed calcification in necrotic areas of the dermis and panniculus. There was an inflammatory infiltrate about the calcium deposits.

The patient developed a cellulitis about the area of biopsy, with resultant fever and leukocytosis. This condition subsided after penicillin and extensive incision and drainage. She was discharged from the hospital unimproved, with diagnoses of scleroderma with Raynaud's phenomenon and calcinosis.

Comment: This patient presented a typical picture of calcification as it may occur in scleroderma. There was no evidence of disturbance of calcium metabolism except at the site of tissue injury.

Case 11. Calcinosis of the circumscript variety appeared in areas of damaged tissue in a 44 year old woman suffering from scleroderma.

Case 12. There was considerable discussion among the clinicians as to whether this patient had scleroderma or rheumatoid arthritis. The extent of the joint changes and the biopsy findings made the latter diagnosis the more tenable one. Again the calcinosis seemed to be the result of lime deposition in injured tissue rather than any primary defect of calcium or phosphorus metabolism.

Analysis of Case Reports Since 1938

Because excellent reviews [2, 6, 7, 11, 24, 27] cover the subject of calcinosis circumscripta and calcinosis universalis up to 1938, this report is concerned only with subsequent literature. Since 1938, there are found in the literature 54 instances [32-77] of calcinosis of the circumscript or universal varieties. If 12 cases from the University Hospital are added, 66 cases of soft tissue calcification can be studied. Primary diagnoses of scleroderma, Raynaud's syndrome or dermatomyositis may be assigned to most of them. Table 1 indicates the distribution of the primary diagnoses in these patients.

Table I

Distribution of Primary Diagnoses of 66 Patients with Calcinosis Circumscripta and Calcinosis Universalis in Whom Blood Serum Concentrations of Calcium and Phosphorus Were Normal

Disease	No. of Patients
Dermatomyositis alone or with features of poikiloderma, lupus erythematosus, scleroderma	24
Scleroderma with or without Raynaud's syndrome	24
Raynaud's syndrome alone	2
Acrodermatitis chronica atrophicans (?late scleroderma)	1
Rheumatoid arthritis	2
"Gout" (?Rheumatoid arthritis)	1
Lupus erythematosus (10 years' duration)	1
Following "chicken pox"	1
No evident primary disease	10
Total	66

If there had been more intensive investigation in the group of 10 patients recorded as "no evident primary disease," some abnormality preceding and responsible for the calcification probably would have been found. In fact, as the records stand, it takes very little reading between the lines in half of these cases to assign diagnoses of dermatomyositis or scleroderma to them. For this reason these cases are not listed as idiopathic calcinosis. This term should be abandoned, since it tends to produce a false sense of satisfaction in a "diagnosis" and prevents proper study for the detection of the primary disease.

If primary disturbances of calcium and phosphorus metabolism are eliminated, it can be seen that there is a predominance of scleroderma and dermatomyositis as causative conditions for calcinosis circumscripta and calcinosis universalis. Although a patient with scleroderma may show widespread

deposits, usually there are only a few. Conversely, a patient with dermatomyositis may show only a few deposits, but much more often widespread calcification is produced. Instead of segregating these patients into the two groups, calcinosis circumscripta and calcinosis universalis, on the basis of the extent of deposited calcium, they are separated into the scleroderma group with calcification and the dermatomyositis group with calcification. Patients suffering from Raynaud's syndrome, acrodermatitis atrophicans chronica, rheumatoid arthritis and lupus erythematosus are included in the scleroderma group.

The scleroderma group contains 34 patients, of which there were four white males and 30 white females. The average age of onset of the primary disease is given as 31. At the time the case was reported, the duration of the disease averaged 16.5 years and the duration of the calcium deposits averaged about 10 years. Four deaths are reported, after 40, 15, 20 and 17 years of the disease. One patient is recorded as dying at the age of 66 of heart failure; one at age 42 following Heller's operation to split the esophagus longitudinally; one at age 70 of a cerebrovascular accident, and the other patient at 66 of bronchopneumonia and renal failure.

The clinical and laboratory features do not differ from those in any other collection of patients suffering from scleroderma, rheumatoid arthritis, acrodermatitis or Raynaud's syndrome, except for the presence of the calcium deposits. The calcifications tend to be small and localized to the hands, feet, elbows, knees, hips and pelvic areas. There is frequently a troublesome inflammatory response about the deposits, and there is a tendency to extrusion of lime salt with subsequent ulceration and scarring. Treatment of many types is ineffective in dissolving the deposits and, if spontaneous disappearance of the deposits occurs, it must be very rare.

Because of differential value, certain features of the scleroderma group are emphasized. There is seldom fever or tachycardia or loss of weight. The white blood count is usually normal, unless there is an inflammatory process about a calcium deposit. Occasionally mild anemia is present. There are no changes in bone in roentgenograms except the osteoporosis of disuse and the bony rarefaction often seen in women of this age group. At times there is the dissolution and spontaneous amputation of bone of the terminal phalanges, as is found in patients with scleroderma, whether calcinosis is present or not. The urinalysis is usually negative, but traces of albumin and a few formed elements may be found. Renal function as measured by the non-protein nitrogen or the urea clearance is normal. The serum phosphorus, calcium and alkaline phosphatase values are normal. Urinary calcium values are within the normal range. Any muscle atrophy or limitation of motion depends upon the location and extent of the scleroderma and is not extreme as in the dermatomyositis group. Skin and muscle biopsies are helpful in establishing a correct primary diagnosis.

The dermatomyositis group of 32 patients includes 11 white males, 18

white females, two colored females and one Indian female. The average age of onset of the primary disease is 15 years. At the time of submission of the reports, the average length of duration of the disease was seven and one-half years, and the average duration of the calcium deposits was five years. It is appreciated that the exact length of time the calcium deposits have been present cannot be established with certainty. There probably are microscopic deposits for some time before the gross accumulations are noticed. Five deaths are reported in this group of 32 patients. One patient died of pneumonia at age 31, two years after the onset of her disease. The second lived for two years after the disease began, and died at age 11 shortly after parathyroidectomy. The third died of pulmonary tuberculosis at age 29, one and one-half years after the onset of her illness.. The fourth patient died at age 14 of acute gastroenteritis after being sick for two years. The fifth patient died three years after the onset of his illness. At the time of death he was 17. Death occurred outside of a hospital, so that the immediate cause of death is unknown.

Aside from the youth of the patients and the tendency for the disease to be severe, there is no essential difference between dermatomyositis with or without calcinosis. The deposition of lime salts in connective tissue is extensive in a well developed case. Tendons, skin, subcutaneous tissue and muscle may be involved. In rare instances the abnormal deposit is found in the kidney. The face and neck are practically always spared. The buttocks, thighs, arms and trunk are prone to accumulate large deposits. Particularly troublesome are the inflammatory reactions about the calcified areas and the large, slowly healing ulcers that frequently form. Contractures, muscle atrophy and failure of an extremity to develop are often extreme. The calcium deposits are often discernible within a few weeks or months after the disease begins. If the patient dies, the outcome is usually related directly to his disease, and death comes about two years after the onset of his illness. Occasionally spontaneous cure of the disease and resorption of the calcium deposits are reported. It seems doubtful that any form of treatment thus far devised has influenced the disease process.

Again because of differential value, certain features of the dermatomyositis group with calcification are presented. Fever, tachycardia and loss of weight are likely to occur. A moderate leukocytosis and a mild eosinophilia are often found. A mild to moderate anemia is the rule. Serum protein abnormalities are likely to be apparent, especially if studied by electrophoretic methods. In about one-third of the cases, urinalysis reveals albuminuria and the presence of formed elements, but renal function is normal as measured by the blood non-protein nitrogen and the urea clearance. Roentgenograms of the bones indicate changes explainable on the grounds of disuse. Values are normal for serum calcium, phosphorus and alkaline phosphatase. Urinary calcium values are within the normal range. Skin and muscle biopsies are often helpful in establishing a primary diagnosis.

In the absence of abnormal values for blood calcium or phosphorus, calcinosis circumscripta and calcinosis universalis are practically always secondary to tissue damage produced by one of the "collagen diseases."

Serum Calcium, Phosphorus and Phosphatase Studies in the Collagen Diseases Associated with Calcification

In general, serum calcium, phosphorus and alkaline phosphatase determinations done singly or at infrequent intervals are reported as normal. In the 66 patients with whom this paper is concerned, there are six instances (cases 2, 41, 49, 68, 69 and 74) in which the calcium or phosphorus values might be considered abnormal. The abnormal values often represent single determinations. It is usually not known whether the results obtained represent deviations from the normal for the laboratory concerned. Therefore, there is no convincing evidence that disturbed blood calcium or phosphorus levels are etiologically related to the calcification. This is in agreement with other authors.[2, 3, 4, 11] It is conceivable that resorption of deposits might temporarily elevate calcium or phosphorus levels.

Metabolic balance studies have been reported by some authors as being normal.[2, 3, 7, 24, 28, 39] Others have indicated that there is a tendency for the organism to retain calcium.[2, 4, 7, 34] It seems that this is to be expected, since the grossly visible calcium deposits must come from somewhere. It does not indicate that there is an abnormality of calcium metabolism remote from the site of the calcification, but only that calcium is being removed from the blood and stored in injured tissue. Other authors report a negative calcium balance, perhaps an indication that calcium is being resorbed at the time of the study.[2, 18]

Prognosis in the Collagen Diseases with Calcification

The prognosis for life, function and cure is that of the primary disease. As previously mentioned, in the scleroderma group the prognosis for life and fair function is good. In the series of 34 patients, death was caused by a disease not directly related to the scleroderma. The calcium deposits rarely, if ever, disappear, though small areas may be extruded or surgically removed.

The dermatomyositis group presents a severe disease likely to result in much disability. Death directly related to the ravages of the disease occurred in about 15 per cent of the 32 patients within three years of the onset of the illness. Partial or complete cure is recorded in a few instances.[38, 47, 71] These recoveries are probably spontaneous, since the results attributed to treatment are sporadic and cannot be repeated by other authors.

Apparently extensive lime deposits can be resorbed if the underlying disease is cured.[2, 5, 7, 10, 16, 17, 18, 24, 25, 26, 28] In this connection, there are instructive experiments dealing with guinea pigs. Van Wagtendonk [29, 30] reported a deficiency disease in which extensive calcium deposits were produced.

Administration of the deficiency factor present in cream resulted in disappearance of the pathologic calcification.

Treatment of the Collagen Diseases Associated with Calcification

Various forms of treatment are reported, all directed toward removal of the calcium deposits.[2, 7, 11, 24] The use of ketogenic diets, ammonium chloride and sodium acid phosphate is recommended, with the idea that the salts of calcium are more soluble in an acid medium. Low calcium diets are employed, in the hope that calcium needed by the organism will come from the abnormal deposits when the dietary source is curtailed. The principle behind heliotherapy and roentgen-ray treatment is not apparent.

All methods of treatment are ineffective. Efforts directed toward the calcium deposits alone are illogical, and it is only when the primary disease can be brought under control that there is any hope of real cure.

Palliative surgical and dermatologic forms of local treatment are indicated when the calcium deposits become secondarily infected, or when a sterile foreign body inflammation is set up.

Differential Diagnosis

Because the nature and location of calcium deposits arising in the course of several pathologic conditions [23] may mimic exactly those occurring in

Table II

Diseases to Be Considered and Laboratory Tests to Be Done When Calcinosis Universalis or Calcinosis Circumscripta Is Found

Disease	Serum Ca	Serum P	Alkaline Phosphatase	Urine Ca	Renal Function	Bone X-Rays
Scleroderma	N	N	N	N	N	Osteoporosis of disuse; amputation terminal phalanges
Dermatomyositis	N	N	N	N	N	Osteoporosis of disuse; small bones of disuse
Raynaud's syndrome	N	N	N	N	N	Osteoporosis of hands
Rheumatoid arthritis	N	N	N	N	N	Osteoporosis of disuse; joint changes
Acrodermatitis chronica atrophicans	N	N	N	N	N	Osteoporosis at times
Hyperparathyroidism	↑	↓	N or ↑	↑	N or ↓	Normal or generalized osteitis fibrosa cystica
Vitamin D intoxication	↑	↑ or N or ↓	N or ↑	↑	N or ↓	Normal or diffuse change
Metastatic bone disease	↑	↑ or N or ↓	↑	↑	N	Localized bone disease
Multiple myeloma	↑ or N	↑ or N	↑	↑ or N	N or ↓	Localized bone disease
Paget's disease of bone	↑ or N	↑ or N	↑	↑ or N	N or ↓	Localized bone disease
Renal failure	N or ↓	↑	↑	N or ↓	↓	Generalized osteitis fibrosa cystica
Pseudohypoparathyroidism	↓	↑	N or ↓	↓	N	Increased bone density; short metacarpal and metatarsal bones

association with the collagen diseases, it is important to consider the differential diagnosis. Particular attention must be given to the serum calcium, phosphorus and alkaline phosphatase levels, to roentgen-ray examination of the bones, to urinary calcium values and to renal function. Table 2 presents these important features in association with the disease entities that may develop widespread soft tissue calcification.

Summary and Conclusions

1. Calcification occurs as a result of either local tissue injury or abnormalities of calcium and/or phosphorus regulation remote from the site of calcium deposition.

2. A classification of pathologic calcification is suggested.

3. Twelve patients manifesting several types of "collagen disease" with secondary calcification are reported.

4. A clinical picture of calcification as it occurs in the "collagen diseases" is presented from combined data involving 66 patients.

5. Calcinosis circumscripta and calcinosis universalis represent descriptive terms rather than primary diagnoses. Calcification of this type may be secondary to a disturbance of factors regulating blood serum calcium and/or phosphorus levels. It may also occur in the so-called collagen diseases as a result of tissue injury.

6. A table is compiled of laboratory and roentgen-ray findings of use in the differential diagnosis of primary disease processes that may result in widespread soft tissue calcification.

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THE ORAL USE OF COMBINED VITAMIN B_{12} AND FOLIC ACID IN TROPICAL SPRUE *

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Soon after the announcement in July, 1945, of the synthesis of *Lactobacillus casei* factor by several investigators [1] at the Lederle Laboratories and the Calco Division of the American Cyanamid Company, it was shown by Spies, Vilter and Koch [2] that this substance possessed a definite hematopoietic effect in patients with macrocytic anemia when administered intravenously, intramuscularly or orally.

In January, 1946, Spies, López, Menéndez, Minnich and Koch [3] reported that the macrocytic anemia of tropical sprue found in Cuba responded in a similar manner. Several other investigators [4, 5, 6, 7, 8, 10] also reported striking improvement of anemia when folic acid was administered to patients with tropical or nontropical sprue.

Even though some authors [11, 12] report no improvement when folic acid is administered to patients with macrocytic anemia of tropical and nontropical sprue, the majority of these patients, according to Spies,[13] show a maximal hematopoietic response when 10 mg. of folic acid are given daily by mouth. This same author states that "a number of patients have failed to respond fully to folic acid at the level of 3 or 4 mg. per day by mouth and have responded to liver extract or yeast administered in amounts which supply 1 mg. or less of folic acid daily." These findings suggest that the antianemic factor present in liver extract or yeast may be a combination of chemical substances, or that it may be a much larger molecule than folic acid.

Meyer [14] reports that, in a few cases of pernicious anemia in relapse, small oral doses of folic acid (5 mg. daily), in addition to 0.5 unit of liver extract, often give a reticulocytosis greater than anticipated, and that with such therapy the remission is complete. The possible enhancing effect of liver extract when combined with folic acid cannot be due to the folic acid content of the former, since 1 unit of liver extract contains only 0.38 μ gm. of folic acid.[15]

That both folic acid and vitamin B_{12} are needed for full hematopoietic response in pernicious anemia is strongly suggested by the observations of Bethell and his co-workers,[16] who found that when a case of pernicious anemia was treated with vitamin B_{12} a maximal response was obtained, but that when a folic acid antagonist was given before and during vitamin B_{12}

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administration the hematopoietic response was delayed and suboptimal. Apparently, when the action of folic acid has been "blocked" by a folic acid antagonist, the patient is unable to respond to vitamin B_{12}.

Davidson and Girdwood [17] have occasionally obtained excellent hematopoietic responses in pernicious anemia with as little as 1 mg. of folic acid by mouth, but found that it fails to cause a neurologic remission or to prevent a neurologic relapse.

In 1944 Castle and his co-workers [18] fed purified casein with various accessory factors of the vitamin B group to patients with pernicious anemia. They included folic acid among the substances administered, but obtained no hematologic or clinical response. However, the quantity of folic acid used was only 2.3 to 3.6 mg. daily. Sharp, Vonder Heide and Wolter [19] failed to obtain any hematologic response, except an increase in the hematocrit reading, when 1.5 mg. of folic acid were fed daily to 10 patients with refractory macrocytic anemia.

The minimal oral dose of folic acid needed to produce an optimal hematopoietic response in tropical sprue has not been determined. Suárez, Spies and Suárez [20] found that a daily oral dose of 10 mg. was adequate to induce a hematopoietic response. They also observed that small daily doses (10 mg. a day) were more effective than 50 times as much given in a single dose. These authors state that, although the oral maintenance dosage of folic acid in tropical sprue has not been established, 2.5 to 5 mg. daily are an adequate dosage in the majority of the cases.

From the above data we can conclude that the minimal dose of folic acid needed to produce a significant hematologic and clinical response when given alone by mouth to patients with sprue or pernicious anemia is in the neighborhood of 5 to 10 mg. daily.

Four years ago, Shorb [21] discovered a new factor in refined liver extracts that was highly potent in promoting growth of the microörganism *Lactobacillus lactis* Dorner. Soon afterwards, Riches et al.[22] isolated a pure crystalline compound from liver and designated it vitamin B_{12}. West [23] proved that this substance possessed the property of inducing a hematopoietic response in patients with pernicious anemia in relapse. Likewise, Bethell,[24] Hall and Campbell [25] and others also showed that the parenteral use of vitamin B_{12} produced a hematologic response similar to that produced by liver extract when given to patients with pernicious anemia in relapse.

Beneficial results from parenteral administration of vitamin B_{12} in tropical and nontropical sprue have been reported by Spies, Suárez and associates.[26]

In regard to dosage, 15 μ gm. once or twice a week intramuscularly seem to be adequate for patients with pernicious anemia in relapse, or for patients with tropical or nontropical sprue. The maintenance dosage appears to be 15 μ gm. every two to four weeks, given intramuscularly.

The oral use of vitamin B_{12} has been studied by several investigators. Castle and associates [27] obtained no response from the oral use of 5 μ gm. of vitamin B_{12} daily, but if gastric juice from a normal person was given simul-

taneously a hematopoietic activity could be induced in patients with pernicious anemia in relapse. Likewise, Hall and Campbell [28] arrived at the same conclusion when the same amount of vitamin B_{12} was given simultaneously with gastric juice from patients with duodenal ulcers to patients with pernicious anemia in relapse.

The minimal oral dosage of vitamin B_{12} necessary to induce a hematopoietic response in pernicious anemia has been studied by several investigators. Meyer and co-workers [29] obtained submaximal reticulocytosis but adequate clinical and hematopoietic response in five patients with pernicious anemia in relapse treated with daily oral doses of 75 to 150 μ gm. of vitamin B_{12} for periods of up to seven months. One patient failed to respond to an oral daily dose of 150 μ gm., and a second one to quantities of up to 250 μ gm. of vitamin B_{12} a day. Both patients responded favorably to subsequent parenteral administration of vitamin B_{12}. Two additional patients were given oral daily doses of 1.67 mg. of folic acid and 25 μ gm. of vitamin B_{12} for five weeks. The reticulocytosis obtained was maximal, and the rise in hemoglobin and red blood cells was rapid. There was early clinical improvement in these two patients. A third case was treated similarly, with adequate response.

Schrumpf [30] treated six verified cases of pernicious anemia with oral vitamin B_{12} and folic acid. The dose administered daily was 10 μ gm. of vitamin B_{12} and 0.67 mg. of folic acid in three cases, and double these quantities in two cases. In one case there was no lasting effect when the smaller dose was used. The author concludes that "the effect of the treatment seems to be fairly consistent with the results obtained with liver extracts." It was found in this study that the increase in hemoglobin was 14 per cent per 10 days using liver extract, and 12.4 per cent per 10 days when vitamin B_{12} and folic acid were used. The reticulocyte response was found to be less pronounced and to occur later than when liver extract was used. The cases with leukopenia and thrombocytopenia showed normal increases in the leukocyte and platelet counts when this dose of vitamin B_{12} and folic acid was employed.

Spies and co-workers [31] have failed to get a hematopoietic response in pernicious anemia using 30, 50, 100 and 400 μ gm. of vitamin B_{12} in single oral doses, but they noted an effect by giving 500 μ gm. once, 800 μ gm. twice, 150 μ gm. for 20 and 27 days consecutively, and 450 μ gm. for 10 daily doses.

From the above clinical experience it can be said that the minimal effective oral dose of vitamin B_{12} in pernicious anemia is 75 to 150 μ gm. daily.

In sprue, vitamin B_{12} has been found to be of some value when given by mouth. As in pernicious anemia, gastric juice seems to potentiate the hematopoietic activity of orally administered vitamin B_{12}. Diéz Rivas, Suárez, Hernández Morales and Pérez Santiago [32] administered vitamin B_{12} orally to 10 patients with tropical sprue. When single doses of 15 to 50 μ gm.

were given to eight patients, an optimal response was obtained in one case, a suboptimal response in five cases, and no response in two cases. Larger single doses of 90 to 450 μ gm. of vitamin B_{12} given orally to four patients with active tropical sprue induced a suboptimal response in one case and none in three cases. Two cases received multiple daily doses of vitamin B_{12}. A hematopoietic response was obtained in each case after the oral dose had been increased to 150 to 200 μ gm. daily. These authors conclude that in tropical sprue the approximate minimal oral dosage of vitamin B_{12} necessary to induce an appreciable reticulocytosis and a definite clinical improvement is 150 to 200 μ gm. daily for a period of at least two to three weeks or longer.

Method of Study

To evaluate the effect of simultaneous oral administration of folic acid and vitamin B_{12} in tropical sprue, an amount of each substance known to have little or no hematopoietic value in this disease was administered daily as a single tablet two hours before breakfast. Each tablet * contained 1.67 mg. of folic acid and 25 μ gm. of vitamin B_{12}.

All the patients were placed on a preliminary sprue diet that contained 3,718 cal/d. and 134.5 gm. of vegetable protein, 568.5 gm. of CHO and 102 gm. of fat. It allowed six ounces of milk a day, and 20 gm. of animal protein were given once or twice a week. The remainder of the protein was obtained from vegetable sources.

Six patients with active tropical sprue were selected for this study. Five of these patients had been treated in the past with either folic acid or liver extract. There were four male and two female patients. The youngest was 19 years old and the eldest 67.

A complete blood count, hematocrit, bone marrow study, reticulocyte count, urine analysis and stool examination were done before treatment was started. During treatment a daily reticulocyte count and a weekly complete blood count with hematocrit were performed. The body weight of each patient, as well as stool counts and daily medical check-ups, with special emphasis on glossitis and the general well being of each patient, was recorded. A bone marrow study was repeated after one week of treatment.

Case Reports

Case 1. This patient, a 67 year old white female, was first seen at the University Hospital in 1946 with a typical picture of tropical sprue. Folic acid was given with good results, and the patient was discharged on 5 mg. of folic acid daily, which was continued for approximately three months. Three years later, on her first return visit to the out-patient department following her hospitalization, she gave a history of recurrence of diarrhea, glossitis, weight loss and anemia. The diet had been very deficient, and she had received no medication during the previous three years. The patient was re-admitted to the hospital and placed on a preliminary sprue diet. Folic acid (1.67 mg. a day) was started orally every morning and was continued for two

* Supplied by E. R. Squibb & Sons.

weeks, without any hematologic improvement. The diarrhea and glossitis continued as on admission. Combined folic acid (1.67 mg./d.) and vitamin B_{12} (25 μ gm./d.), as a single tablet, were then given every morning. Under this medication the megaloblastic bone marrow reverted to normal and a reticulocytosis of 16.2 per cent occurred. By the fifth day of treatment, the hemoglobin had increased from 42.5 per cent to 62.5 per cent.

Two weeks after the start of this medication the patient felt better, her appetite had returned, the glossitis had disappeared and the number of stools had decreased from five to six watery stools a day to one or two soft stools daily. The patient was discharged on one tablet of combined folic acid and vitamin B_{12} every morning. Three months after discharge there was no glossitis or diarrhea. The appetite was good and the patient gained three pounds in spite of a poor diet at home. Eight months after discharge the hemoglobin was 95 per cent, there was no diarrhea or glossitis, and the weight had increased to 105 pounds (a total gain of 17 pounds).

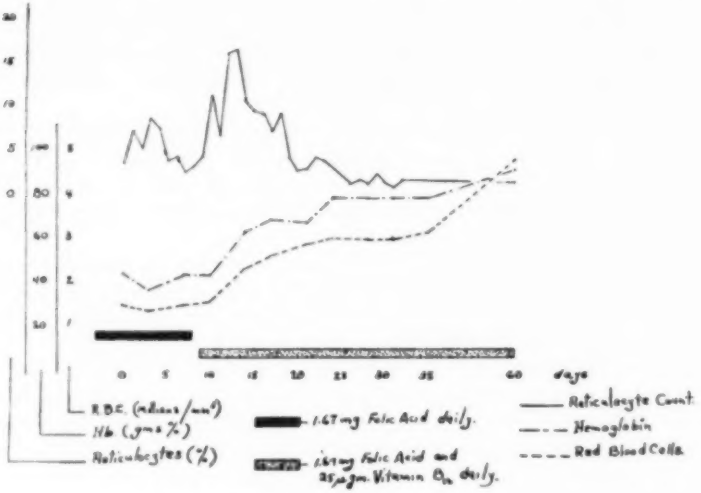

FIG. 1. Case 1.

Case 2. This 48 year old white male was hospitalized with a relapse of sprue. He had had the disease for about 13 years, during which time he had received treatment with folic acid and liver extract. For the previous two years he had been taking one to three tablets of folic acid daily. In spite of folic acid therapy he developed progressive weakness, pallor and diarrhea. The hemoglobin decreased to 39 per cent. He was re-admitted and given 15 mg. of folic acid daily for a period of three weeks, without any hematologic or clinical improvement. The megaloblastic bone marrow persisted. Combined folic acid and vitamin B_{12} were started, and on the ninth day of treatment a reticulocytosis of 17 per cent occurred. The megaloblastosis of the bone marrow decreased on the eleventh day of treatment. The patient was discharged in good condition. Follow-up in the out-patient department has been continued to date. Six months after discharge the hemoglobin had increased from 42.5 per cent to 77.5 per cent, and the red blood cell count from 1.15 million to 4.14 million

cells per cubic millimeter. The volume of packed cells was 39 per cent and the MCV had decreased from 120 cubic micra to 95 cubic micra. The general condition of the patient was satisfactory, and the diarrhea as well as the glossitis disappeared.

Case 3. This patient who had had tropical sprue for two years, had been previously treated successfully with liver extract. He was readmitted with a relapse of sprue. Ten milligrams of folic acid daily by mouth had failed to induce a hematologic response. While on this form of treatment the hemoglobin had decreased from 60 per cent to 47 per cent after three weeks of folic acid therapy. Combined folic acid and vitamin B_{12} were started and on the tenth day of treatment a reticulocytosis of 15.2 per cent occurred. The hemoglobin increased from 47 per cent to 87.5 per cent. The glossitis and the diarrhea that had been present on admission gradually disappeared.

Case 4. This 28 year old white female patient was admitted to the hospital with diarrhea, glossitis and macrocytic anemia. There were 4.8 per cent megaloblasts in the bone marrow on admission.

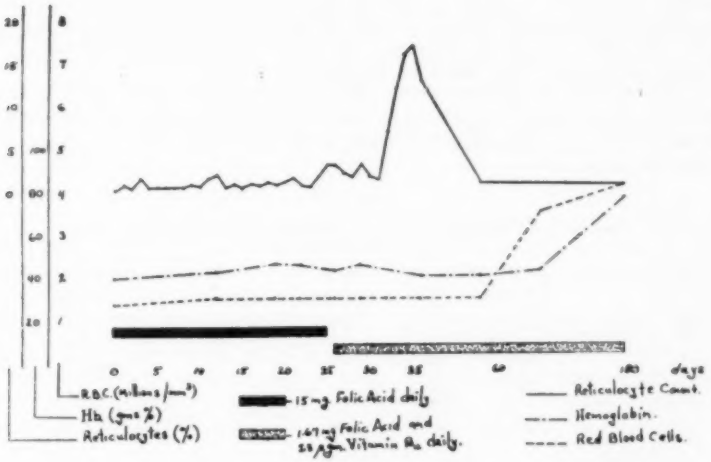

FIG. 2. Case 2.

The patient had had bilharziasis in the past that was successfully treated with Fuadin. Liver extract had been used prior to admission, the last injection having been four months previously.

Combined folic acid and vitamin B_{12} were started (1.67 mg. folic acid and 25 μ gm. of vitamin B_{12}/day) soon after admission. On the eighth day of treatment the patient's reticulocyte count rose to 3.4 per cent. Even though the reticulocyte count never increased beyond this level, the hemoglobin increased from 65 per cent to 90 per cent in two weeks. The diarrhea and glossitis disappeared one week after treatment had been started. There was a gain in weight of 25 pounds in two months. On discharge the hemoglobin had increased to 102.5 per cent and the red blood cell count had risen from 2.43 millions to 4.4 millions per cubic millimeter during this period. The MCV decreased from 133 to 102 cubic micra.

Case 5. This 38 year old white male had had a previous admission (four years earlier) at which time he had complained of diarrhea, glossitis and 10 pound weight

loss. He was found to have a macrocytic anemia and a flat glucose tolerance test. The blood serologic test for syphilis was positive.

Two months prior to re-admission these same symptoms recurred. On his second admission, he was found to have 6.2 per cent megaloblasts in the bone marrow; the hemoglobin was 40 per cent and the MCV was 147 cubic micra. The red blood cell count was 1.36 millions per cubic millimeter.

Combined folic acid and vitamin B_{12} (1.67 mg. of folic acid and 25 micrograms of B_{12}) were administered every morning. The patient had been placed on a preliminary sprue diet on admission. On the seventeenth day of treatment a reticulocytosis of 16 per cent occurred. The hemoglobin increased from 40 per cent on admission to 49 per cent, and the red blood cell count rose from 1.36 millions to 1.78 millions per cubic millimeter two weeks after treatment had been started. After four weeks of treatment the hemoglobin had risen to 70 per cent and the red blood cell count to 2.94 millions per cubic millimeter. The MCV decreased from 147 to 114 cubic micra in four weeks of therapy. During this period of time the patient gained 18 pounds in weight, and the glossitis as well as the diarrhea disappeared. Three months after discharge the hemoglobin was 107.5 per cent and the red blood cell count was 5.24 millions per cubic millimeter. The MCV was now 96 cubic micra. The weight had increased 28 pounds since the start of treatment.

Case 6. This 19 year old white male patient, who had had tropical sprue for three years, was found on admission to have a hemoglobin of 67.5 per cent and a red blood cell count of 2.69 millions per cubic millimeter. The MCV was found to be 123 cubic micra.

TABLE I

Hematological Results of Combined Use of Folic Acid and Vitamin B_{12} Therapy in Tropical Sprue

Name Age	Type of Oral Medication	Hemoglobin (%)			RBC×10⁶			Reticulocytes (%)					M.C.V. (cu.μ.)		
		Initial	14th Day	Final Day	Initial	14th Day	Final Day	Initial	7–10 Day	Final	% Peak	Day of Peak	Initial	14th Day	Final Day
1. I. D. 67	Folic Acid, 1.67 mg./d.	30	42.5	42.5 (20 d.)	1.39	1.4	1.4	4	3	3	8.2	5	130	135	135
	Folic Acid, 1.67 mg. and 25μ gm./d. Vit. B_{12}	42.5	65	90 (90 d.)	1.42	2.79	4.79	4	9.2	1.2	16.2	5	135	118	87
2. H. R. 49	Folic Acid, 15 mg./d.	39	42.5	42.5 (25 d.)	1.39	1.56	1.5	0	.6	1	1.8	8	133	120	120
	1.67 mg. F.A. and 25μ gm. B_{12}/d.	42.5	40	77.5 (210 d.)	1.5	1.52	4.14	1	3	.7	17	23	120	120	95
3. E. M. 46	10 mg. F.A./d.	60		47 (36 d.)	2.02		2.03						145		125
	1.67 mg. F.A. and 25μ gm. B_{12}/d.	47	65	87.5 (78 d.)	2.03	2.63	3.96	1.6	5	8	15.2	10	125	133	102
4. P. V. 28	1.67 mg. F.A. and 25μ gm. B_{12}/d.	64	90	102.5 (58 d.)	2.43	3.1	4.4	0	3.4	.8	3.4	8	133	141	102
5. E. C. 38	1.67 mg. F.A. and 25μ gm. B_{12}/d.	40	49	70 (30 d.)	1.36	1.78	2.94	0	8	1	16	17	147	129	114
6. H. E. 19	1.67 mg. F.A. and 25μ gm. B_{12}/d.	67.5		87.5 (40 d.)	2.69		4.17	1.2	5	1.2	5	1.2	123		103

On the sixth day of combined folic acid and vitamin B_{12} (1.67 mg. of folic acid and 25 μ gm. of vitamin B_{12} per day by mouth), a reticulocyte peak of 6.2 per cent occurred. Forty days after start of treatment the hemoglobin had increased to 87.5 per cent and the red blood cell count to 4.17 millions per cubic millimeter. The MCV decreased from 123 to 103 cubic micra. There was a gain in weight of 31 pounds after four months of therapy. The glossitis and the diarrhea disappeared.

Discussion

In tropical sprue, as in pernicious anemia, the macrocytic anemia, the megaloblastic bone marrow and the diarrhea, as well as the glossitis and weight loss, can be corrected by either folic acid or vitamin B_{12} preferably when these substances are used parenterally. In both of these diseases these same substances are effective when given by mouth in the proper dosage.

The minimal effective dose of folic acid capable of inducing a satisfactory hematologic response in either tropical sprue or pernicious anemia appears to be 10 to 15 mg. daily when given by mouth. Vitamin B_{12} has also been found to have beneficial effects on the anemia of tropical sprue and pernicious anemia when given by mouth in rather large doses. The minimal oral daily dose of vitamin B_{12} needed to induce a satisfactory hematologic response in either tropical sprue or pernicious anemia has been found to be in the range of 150 to 200 micrograms.

When folic acid and vitamin B_{12} are given simultaneously by mouth in either pernicious anemia or tropical sprue, the hematologic response is augmented considerably. It has been found that 1.67 mg. of folic acid or 25 micrograms of vitamin B_{12} are not effective in correcting the anemia in either of these conditions in the majority of cases; but when these suboptimal amounts of folic acid and vitamin B_{12} are given simultaneously by mouth daily to patients with either tropical sprue or pernicious anemia, a response comparable to parenteral liver extract therapy is obtained in the majority of the cases.

It appears, therefore, that the macrocytic anemia of tropical sprue or pernicious anemia is a multiple deficiency state, and that both folic acid and vitamin B_{12} are necessary to correct this abnormality of hematopoiesis. The synergistic action of folic acid and vitamin B_{12} (extrinsic factor), or vice versa, suggests the possibility that folic acid is needed for the proper absorption and utilization of vitamin B_{12} by the human organism.

The extrinsic factor as described by Castle may very well be a combination of substances, among which folic acid and vitamin B_{12} play a prominent rôle.

Summary and Conclusions

1. Six cases of tropical sprue in relapse have been treated with combined folic acid and vitamin B_{12} orally. Folic acid (1.67 mg.) and vitamin B_{12} (25 μ gm.) were administered simultaneously in tablet form every morning.

2. In each case, a satisfactory hematologic and clinical response was obtained with this medication.

3. The results obtained from this form of therapy in tropical sprue compare favorably with the hematopoietic effect of parenteral liver therapy in this disease.

4. Folic acid potentiates the hematopoietic effect of orally administered vitamin B_{12} in cases with tropical sprue in relapse.

5. When daily doses of either 1.67 mg. of folic acid or 25 μ gm. of vitamin B_{12} are given orally to patients with tropical sprue in relapse, no hematopoietic effect is obtained. Simultaneous administration of these same amounts of folic acid and vitamin B_{12} produces an optimal hematopoietic response in this disease.

6. It can be concluded that in tropical sprue, as in pernicious anemia, there is a deficiency of both folic acid and vitamin B_{12}, and that the mechanism of absorption and utilization of these two substances is similar in both diseases.

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THE EFFECT OF PENICILLIN ON THE RENAL LESIONS OF SUBACUTE BACTERIAL ENDOCARDITIS *

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THE use of antibiotics, in particular penicillin, in the treatment of subacute bacterial endocarditis has so altered the course of the disease that infection is arrested in all but 10 per cent of cases treated. Only about 10 to 20 per cent die from the complications of the disease itself. The exact rôle of the renal lesions as a cause of death in treated cases of subacute bacterial endocarditis is still not settled. A report by Christie [1] on 269 patients treated with penicillin listed 73 deaths of which 8 were due to uremia. However, in a study by Pillsbury and Fiese [2] on 31 patients in which there was an average follow-up period of 35 months for the surviving group there was no clinical evidence of continuing renal lesions in the surviving group and none of the deaths was attributed to renal failure. This study is an attempt to evaluate the effect of penicillin on the incidence of the renal lesions in subacute bacterial endocarditis. This study is based entirely on a necropsied group of cases.

Three types of renal lesions may be present in subacute bacterial endocarditis. These are focal embolic glomerulonephritis, diffuse glomerulonephritis (acute, subacute, and chronic), and renal infarcts. These may occur simultaneously or independently. This report is concerned primarily with diffuse glomerulonephritis, only secondarily with focal embolic glomerulonephritis, and not at all with renal infarcts.

It has been well established that diffuse glomerulonephritis of the acute, subacute, or chronic variety occurs with some degree of frequency in subacute bacterial endocarditis. However, in order to determine the effect of antibiotics on the incidence of this lesion it was necessary to review untreated cases in order to establish an adequate control figure. Table 1 represents an unpublished study by one of the authors of the incidence of diffuse glomerulonephritis in 10,000 consecutive postmortem examinations at another institution. (See table 1.)

In this study glomerulonephritis was present in almost the same incidence in the general run of autopsies as in rheumatic heart disease without associated subacute bacterial endocarditis. It was only when rheumatic cardiovascular disease was complicated by subacute bacterial endocarditis that the

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incidence of glomerulonephritis rose significantly. Thus it would appear that diffuse glomerulonephritis occurs with no greater frequency in rheumatic heart disease than in the general autopsy population. This is in agreement with Baehr and Schifrin [3] but at variance with the reports of Hartman and Bland,[4] and Ehrström.[6]

TABLE I

Autopsy Incidence of Diffuse Glomerulonephritis in Untreated Subacute Bacterial Endocarditis

	No. Cases	Diffuse	Focal
All autopsies	10,000	169 (1.69%)	—
Rheumatic heart disease	320	5 (1.56%)	0
Subacute bacterial endocarditis	125	37 (29.5%)	41

This report is based on a study of 77 consecutive necropsied cases of subacute bacterial endocarditis of which 25 were treated with antibiotics. Thirty-three per cent of the untreated cases had diffuse glomerulonephritis. This is in agreement with the group of cases mentioned before. Not a single treated case had anatomic evidence of this lesion. The incidence of focal embolic glomerulonephritis in this series of cases was 50 per cent lower in the treated group as compared with the untreated group. On the average, antibiotic therapy was started within one and one-half to two months from the onset of the first recognizable signs and symptoms of subacute bacterial endocarditis. The early institution of treatment may be an important factor in the elimination of these renal lesions. (See table 2.)

TABLE II

Comparison of the Autopsy Incidence of the Renal Lesions in Penicillin Treated and in Non-Penicillin Treated Subacute Bacterial Endocarditis

	No. Cases	Glomerulonephritis				Focal
		Acute	Sub.	Chronic	Total	
Non-treated	52	5	6	6	17 (33%)	25 (48%)
Treated	25	0	0	0	0	6 (24%)

Comparison of the duration of the disease, the age, and the incidence of the various types of underlying cardiovascular disease revealed no significant difference in the two groups of cases (treated and untreated). These, therefore, could not be factors that might account for the difference in the rate of occurrence of the renal lesions. (See table 3.)

The type of bacteria involved also did not appear to be a factor. About the same percentage of cases in both groups had *Streptococcus viridans* as the etiologic agent. However, it was interesting to note that in the non-treated cases with renal lesions the incidence of *Streptococcus viridans* as

TABLE III

Age, Underlying Cardiovascular Disease, Duration of Disease in Treated and Non-Treated Cases

	No. of Cases	Age	Type of Heart Disease			Duration of S. B. E.
			Rheumatic	Cong.	Other	
Treated	25	43.5	21	3	1	8 months
Non-treated						
a) with no glomerulonephritis	35	41.5	23	8	4	6 months
b) with glomerulonephritis	17	41.0	13	4	0	7 months

the etiologic agent assumed less importance whereas the rôle of other bacteria such as hemolytic streptococcus, gram-negative bacillus, undifferentiated micrococcus, *Neisseria gonorrhoeae*, and non-hemolytic streptococcus assumed greater importance. This latter fact has implications concerning the etiology of diffuse glomerulonephritis that are beyond the scope of this present report. (See table 4.)

It would seem, however, that this observation would tend to support the view that the mechanism concerned in the production of glomerulonephritis is more important than any single specific organism involved. The mechanisms that have been described by Sarre are concerned with nephrotoxic antigen-antibody reactions. It would appear from this report that diffuse glomerulonephritis associated with subacute bacterial endocarditis is a distinctly different disease in its mechanism of development than diffuse glomerulonephritis which is not associated with subacute bacterial endocarditis in spite of the histopathologic similarity of both lesions. In the former the persistence and progression of the lesion is apparently dependent upon the continued presence of the inciting organism because eradication of the organism eliminates the lesion. In the latter type of glomerulonephritis, evidence exists that the continued presence of the organism (a hemolytic streptococcus) is not needed for persistence and progression of the disease.

In the 25 treated cases of subacute bacterial endocarditis postmortem examination indicated that the valvular vegetations in four cases were still active with little or no evidence of healing, 10 had evidence of considerable

TABLE IV

Bacteria Involved

	Strep. viridans	Other	None
Treated	18	7	0
Non-treated			
Non-renal	25	7	3
Renal	7	8	2
Total	50	22	5

healing, and 11 appeared to be completely healed. The causes of death in these cases were congestive heart failure in 10 and the consequence of embolic episodes in the other 15. Seven of the cases had ruptured valve cusps. Obviously none died as a result of renal insufficiency. In the non-treated group although 17 cases had evidence of diffuse glomerulonephritis and 25 had focal embolic glomerulonephritis, nine cases died as a result of uremia (one of these was on the basis of focal embolic glomerulonephritis).

Conclusions

1. Antibiotic therapy appears to decrease significantly the incidence of diffuse and embolic glomerulonephritis in subacute bacterial endocarditis.

2. In the penicillin treated group of cases diffuse glomerulonephritis was entirely absent and focal embolic glomerulonephritis was reduced in incidence by 50 per cent.

3. In the cases with focal embolic glomerulonephritis there was greater evidence of healing of this lesion in the treated than in the non-treated group.

4. The fact that antibiotic elimination of the organism significantly eliminates diffuse glomerulonephritis associated with subacute bacterial endocarditis would indicate that this is an entirely different disease from diffuse glomerulonephritis unassociated with subacute bacterial endocarditis. In the latter continued presence of the organism is not necessary for progression of the lesion.

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CASE REPORTS

STREPTOCOCCAL MENINGITIS FOLLOWING DIAGNOSTIC LUMBAR PUNCTURE *

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Since the introduction of lumbar puncture as a diagnostic procedure, occasional cases of septic meningitis secondary to this manipulation have been reported. It is generally considered to be an extremely rare complication, despite the large number of lumbar punctures that are performed.

Case Report

A 35 year old unemployed white man was admitted to Brown Hospital, Dayton, Ohio, at 3:00 a.m., April 7, 1949, complaining of severe headache and backache. Approximately 17 hours prior to admission the patient had had a diagnostic lumbar puncture, which had been done to evaluate the status of central nervous system syphilis. He felt well until 12 hours afterward, when he noted the onset of headache which gradually increased in severity. He was seen by a physician at that time and was a given a sedative drug and aspirin. The pain continued to increase in intensity, however, and a backache developed which involved the entire spine. His neck became stiff and he began to have shaking chills. Again the physician was called, and at this time a clinical diagnosis of meningitis was made.

Past History: The patient had had a primary chancre in 1944. Antiluetic treatment was started immediately and continued for 10 months, after which serologic tests for syphilis were reported to be negative. In 1947, he developed weakness and numbness in the legs. A diagnosis of meningovascular syphilis with transverse myelitis was made at that time. He subsequently had several hospital admissions because of his syphilis, and had various types of therapy, including malaria, penicillin and arsenicals. A spastic paraplegia of the legs and a marked urinary incontinence were the residuals at the time of the present admission.

Physical Examination: The patient was a well developed, well nourished young white man, appearing acutely ill. The temperature was 102° F., the pulse 84, and the respiration 18. Active motion of the head caused the patient to cry out with pain. A few expiratory wheezes were heard in both lung bases. Neurologic examination revealed hyperactive reflexes, with sustained bilateral ankle and patellar clonus. The Babinski reaction was positive bilaterally, and the Kernig and Brudzinski signs were positive.

Laboratory Findings: Upon admission a lumbar puncture was performed. The pressure was 420 mm. The fluid was grossly cloudy but flowed freely. The cell

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count of the spinal fluid was 495 white cells per cubic millimeter, of which 98 per cent were polymorphonuclear leukocytes. The sugar content of the spinal fluid was 21 mg. per cent. The gold curve was 1111111100, and the Kahn reaction was 4 plus. A gram stain of the fluid revealed occasional gram-positive cocci, singly and in pairs. A culture proved the organism to be *Streptococcus micro-aerophilia.* The urinalysis was negative. The red blood count was 4.6 million, with 14 gm. of hemoglobin. The white blood count was 22,150, with 82 per cent neutrophils, 12 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophils. Serologic tests for syphilis revealed a 4 plus Kahn reaction, a 4 plus complement fixation and a 2 plus Kline reaction.

A report on the spinal fluid obtained from the lumbar puncture done 17 hours prior to admission was negative except for a 4 plus Kahn reaction.

Course in Hospital: Penicillin therapy was begun with an initial intrathecal injection of 15,000 units in 7.5 c.c. normal saline and a dosage of 1,000,000 units every two hours intramuscularly.

Six hours after admission the patient was semi-stuporous and disoriented, responding very slightly to voice stimuli. He remained in this condition until the following day, when he became rational and more alert and coöperative. He continued to complain of severe headaches. The temperature had dropped rapidly to normal. Marked Kernig's and Brudzinski's reactions persisted. A lumbar puncture done at this time revealed grossly cloudy fluid. This fluid contained 9,800 cells per cubic millimeter, of which 84 per cent were polymorphonuclear leukocytes and 16 per cent lymphocytes. The sugar content of this specimen was 54 mg. per cent. A smear revealed occasional gram-positive cocci, in pairs and short chains. Culture of this fluid produced no growth. Ten thousand units of penicillin in 5 c.c. of normal saline were given intrathecally.

The patient continued to improve slowly. There was a secondary rise of temperature to 99.8° F. on the second day of admission, which quickly subsided, and after the third day the patient remained afebrile. A lumbar puncture done five days after admission revealed clear spinal fluid. The cell count was seven, consisting of four lymphocytes and three polymorphonuclear leukocytes. The sugar was 58 mg. per cent. A smear and culture were reported as negative.

Penicillin therapy was continued until the fourth hospital day. A total of 48,000,000 units of penicillin was given intramuscularly and 25,000 units in 12.5 c.c. of normal saline intraspinally. The patient became ambulatory on the sixth hospital day and had an uneventful convalescence except for a mild urticaria, which was readily controlled with an antihistamine drug. It is interesting to note that the urinary incontinence which had been present since 1947 disappeared within a period of four days. He was discharged on the seventeenth hospital day. Five weeks later the patient was quite well except for his slight paraplegia. The incontinence had not recurred.

Discussion

We have been able to find only 15 cases in the literature in which a proved septic meningitis appears to have been a direct outcome of a diagnostic lumbar puncture.[1, 2, 3, 4, 5, 6, 7] This does not include a certain number of cases in which a meningitis developed following spinal anesthesia. In these cases, however, the causal relationship is quite apparent. Wieder [8] stated that one case of meningitis occurred in 2,700 diagnostic lumbar punctures performed in the Department of Dermatology and Syphilology of the University of Michigan Hospital. Siebert [9] mentions one case occurring in 4,700 taps. His case, however, was unusual. The needle was broken during the procedure and an epidural abscess resulted. This later perforated into the spinal canal, causing the meningitis.

Frequent references were encountered in the literature in which an irritative, noninfectious meningeal reaction was noted to have occurred shortly after a lumbar puncture. All of these cases quickly subsided. Although there was a considerable increase in the cellular elements of the spinal fluid, in none of them was the sugar content lowered and in no case was an organism recovered. These cases have been discussed adequately elsewhere, and we have not included them in our survey.

The mechanism by which a virulent organism can be carried to the meninges by means of a lumbar puncture has been a subject for some speculation. Probably several routes are possible. Several authors [10] have made observations indicating that meningitis is an occasional sequela of a lumbar puncture performed during a septicemia. It has been noted [10] that, in the experimental animal, a lumbar puncture done within a few minutes of the injection of a large quantity of virulent organisms into the blood stream will almost invariably result in a meningitis due to the injected organism. The mechanism is largely obscure, but the theory has been advanced that the sudden lowering of the spinal fluid pressure in some manner breaks down the blood brain barrier. Another hypothesis is that the needle, passing through small venous or capillary channels, carries organisms in the circulating blood directly to the meninges at the site of injection. Wegeforth and Latham [11] presented five cases in which a meningitis developed shortly after a lumbar puncture was done during a septicemia. Remsen [12] has presented a similar case. Pray,[13] however, did not think that this was a significant factor in the causation of meningitis, and stated that the incidence was no greater among patients with bacteremia who were subjected to a lumbar puncture than among those upon whom no diagnostic tap was performed. He did say, however, that there might be very occasional exceptions to this. One cannot say that the occurrence of the meningitis in the above cases was not merely a coincidence.

In the remaining cases reviewed, and also in our own case, there was no preexisting septicemia. The organisms, therefore, must have been introduced into the spinal canal by means of the needle. This was either improperly sterilized or was contaminated as it passed through the skin by organisms which had not been eradicated by the ordinary means of antisepsis. In our own case, we are inclined to believe that the latter was the source of the infection. We were able to obtain all of the remaining lumbar puncture trays which had been sterilized in the autoclave at the same time as the tray used on our patient. Since no organisms were cultured from the articles on the remaining trays, we felt that the possibility of the contaminated needle was very slight, although it could not be ruled out completely.

Summary

A young man in good health was subjected to a routine diagnostic lumbar puncture. Within 18 hours he developed a case of acute infectious meningitis due to *Streptococcus micro-aerophilia*, which subsided on massive penicillin therapy. The incidence of this complication and possible mechanisms are discussed.

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GASTRIC ULCER OCCURRING IN A PATIENT AFTER LOBOTOMY *

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DURING the past year we have observed the appearance of a chronic, non-healing gastric ulcer of the lesser curvature in a patient who had had bilateral prefrontal lobotomy performed 10 months previously.

CASE REPORT

A single white male was admitted to the Veterans Administration Hospital in Canandaigua, New York, on January 1, 1943, at the age of 37 years. His early life had been spent in an orphanage, from which he was adopted at the age of 12 by his present guardian foster parents. He finished the eighth grade at the age of 15 and worked as a farm laborer until he joined the Army in July, 1927, at the age of 21. He remained in the Army after his original enlistment, eventually attaining the grade of staff sergeant in 1938. His mental illness apparently began soon after this promotion. He had a feeling of inadequacy about his new responsibilities. He no

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longer felt the comforting companionship of his former "buddies," who were now his subordinates. These feelings were intensified by the Pearl Harbor disaster, for on December 15, 1941, we find him first admitted to the sick list in Iceland for two weeks because of "nervousness and irritability." He became frankly psychotic six months later. From that time on he remained under psychiatric care in Army hospitals until his transfer to the care of the Veterans Administration.

On arrival at Canandaigua he was found to have auditory hallucinations and to be suicidal. During the following three years his behavior was psychotic, with the pattern of auditory hallucinations, attempts at self destruction and impulsive assaultive action against male patients and attendants. Electric shock courses were followed by only brief remissions. On one occasion he broke five windows and severed his right ulnar artery and some tendons at the wrist. After detailed study and preparation, prefrontal lobotomy was recommended.

On April 22, 1948, after preliminary studies, Dr. E. G. Krueger performed a bilateral prefrontal lobotomy at the Bronx Veterans Hospital. Among the studies was a gastric analysis. This gave a return of 40 units of free HCl and 60 units of total acid; the nature of the stimulus used was not stated.

The patient's postoperative course was uneventful. After the operation he still admitted hearing "the voices" but they no longer disturbed him. He did not manifest the bulimia and marked weight gain sometimes noted after lobotomy. On May 25, 1948, he returned to Canandaigua. His behavior was in striking contrast to the preoperative pattern. He was calm and, although he had little initiative, was assigned to one of the quiet wards, where he soon obtained a pass to circulate about the buildings and courtyard. Persistent attempts were made to have him participate in certain social and educational activities, including exercises to improve the use of his disabled right hand. For reasons which are not clear, he voluntarily surrendered his pass and chose to return to his own ward kitchen detail to work with the female kitchen help, whom he had known and toward whom he felt friendly.

It was at about this time that he first complained of gastric symptoms. The nurse's notes of December 15, 1948, mention that he complained of having "gas on the stomach." On February 8, 1949, he stated that he had epigastric pain, which was relieved by belching and rhubarb and soda. It also awoke the patient at 4:00 a.m. There was no radiation of the pain or vomiting.

Examination revealed a slender, mild mannered man of 42 years. Aside from the lobotomy scar and the residual deformities of his wrist laceration, the physical findings were within normal limits. There was no area of epigastric tenderness. The liver was not enlarged and the spleen was not palpable. The blood count was normal. Stools were negative for occult blood. Fasting gastric analysis showed 19 units of free HCl and 28 units of total acid. Gastrointestinal x-ray series revealed an ulcer on the lesser curvature of the stomach at the angulus.

The patient was placed on the usual ulcer regimen and put to bed in the infirmary. He soon became symptom free. The ulcer showed evidence of healing in the films taken on March 25, but those taken on April 15 revealed a larger crater, despite the fact that the patient had remained symptom free and had been kept in the infirmary under close supervision and on a strict diet.

Believing that we were dealing with a neoplastic ulcer, despite its benign appearance in the films, we decided to explore the patient. On May 2, 1949, a subtotal gastrectomy was done by Dr. Samuel J. Stabins. An indurated ulcer was found on the lesser curvature of the stomach, close to the antrum.

Pathologic examination was made by Dr. Gustav Selbach. "The specimen consists of part of the stomach and the beginning of the duodenum; the whole measuring 12 cm. in length. A lesion measuring 1 by ¾ cm. is found on the lesser curvature about 3 cm. from the pylorus. The lesion extends into the superficial part of the

muscularis. The edges are rather well circumscribed and not ragged. Some induration is present around the edges and base.

"Microscopic examination reveals the base of the ulcer covered by fibrinous exudate, resting on granulation tissue, which is abundantly infiltrated with eosinophiles, leucocytes and lymphocytes. The superficial layer of the muscularis shows some replacement fibrosis. Subintimal connective tissue proliferation and thrombosis are noted in the blood vessels at the base of the ulcer. Diagnosis: Gastric ulcer."

Repeated examinations of the tissue blocks failed to show any malignant cells.

The patient made a satisfactory convalescence from his gastrectomy, except for a short episode of pulmonary atelectasis which cleared up in 48 hours. He has had no symptoms of any sort since the operation. The postoperative films showed good function of the stoma. He at first gained some weight, but is now five pounds under his preoperative weight. His appetite is only fair, and it is difficult to induce him to take additional nourishment between meals. On September 18, while on grounds parole, he took an unauthorized leave of absence and was found at the home of his foster parents, having hitch-hiked there, a distance of about 250 miles.

The psychiatric aspects of the case are to be reported in greater detail in a subsequent paper from this institution. The following excerpts are from a summary note dated October 28, 1949, by Dr. Romano:

"This man has changed since his lobotomy. He remains psychotic. He remains inadequate; he remains to a lesser degree a socially dependent human being. However, he is less impulsive; he is less dangerous to himself and to others and, I believe, has very limited potentialities for progress in the direction of greater independence.

"It is interesting to note that the symptoms of gastric distress occurred at a period in this person's life, when some of the psychotic maladaptive devices, which he had been using up to that time, were being used less intensively. Furthermore, it was at a time when certain measures were being taken to promote increasing social responsibility. Whether these two phenomena have anything to do with the development of his ulcer at this time can only remain conjectural. Current understanding of the psychologic and social adaptive devices utilized by the patient with gastroduodenal ulcer is incomplete if it considers compensatory overactivity as the only manifestation of behavior. After all, peptic ulcers occur in many individuals who are unsuccessful, dependent, parasitic—and they often occur at times when their dependent needs are threatened."

Discussion

There is a considerable body of evidence that the frontal lobe exercises control over gastrointestinal function. Watts and Fulton [1] found that stimulation in certain areas of the prefrontal cortex of monkeys relaxed the stomach sphincters and, in some experiments, caused increased secretion of gastric juice. It was their belief that both excitatory and inhibitory controls were represented in the prefrontal areas. Sheehan [2] reported that "faradic stimulation of both frontal and prefrontal areas gave rise to inhibition of peristalsis (of the stomach of monkeys), but no change in the general level of the intragastric pressure." This occurred only in those animals which had been fed; no change was noted in the unfed animals. Hesser, Langworthy and Kolb [3] noted increased tonus of the stomach wall and marked increase of the amplitude of gastric contractions in cats following bilateral removal of the motor cortex. Bailey and Sweet [4] stimulated the orbital surface of the frontal lobe of monkeys and obtained a "brisk diminution of tonus in the gastric muscles." Following localized frontal excisions in the cat, Mettler [5]

noted increased gastric acidity and motility, and the appearance of ulcers along the lesser curvature. The illustration of the gross and microscopic views of this ulceration in a cat killed 32 days after bilateral frontal lobe ablation is most interesting. It is a true round chronic peptic ulcer, with a dilated central arteriole leading to its base. The arteriole is filled with detritus.

In spite of the now enormous literature on the effect of prefrontal lobotomy in human subjects, there is little mention of altered gastric function. Apparently humans do not die of marasmus, like cats, who develop late relaxation of pyloric tone with anorexia.[5] Indeed, the opposite seems to be true; most authors mention that bulimia is common, and a gain in weight the usual late result.

Petersen and Buchstein [6] studied the gastric response to histamine stimulation before and after lobotomy in five subjects. Four showed a "marked increase in HCl and a prompter response to histamine." The other patient had a hyperacidity before operation, and showed postoperatively a diminished free HCl secretion. Reed [7] has reported similar findings in nine patients, using an Ewald meal before and after lobotomy. Sweet and his colleagues [8] have reported the only case of human peptic ulceration following surgery in this area of the brain that we have been able to find. Their patient was a woman who had melena and hematemesis beginning on the fifteenth postoperative day. She died on the thirty-fourth postoperative day. At autopsy there were several esophageal erosions, but none in the stomach or duodenum. There were also ulcers in the small intestine and colon and rectum. The electrolyte disturbance in this patient was striking.

The physiologic aspects of frontal lobotomy and of topectomy are the subject of intensive study by the Columbia-Greystone Associates.[9] Heath, Carpenter, Gass and Weber, of this group, studied the effect of prefrontal lobotomy on gastric acidity in eight patients, using the histamine test.[10] Five of the eight showed increases in free HCl in the second week after lobotomy. However, of the three who showed lower free HCl values, only one had a lower total acid response. Another group investigated the changes in gastric motility, using a barium progress meal. With one exception, all of these same eight subjects exhibited more rapid gastric emptying after lobotomy.

Carpenter [11] has recently reviewed the data of the Columbia-Greystone Associates as applied to topectomized individuals. He has generously allowed us to look over his data and the draft of his paper. He was unable to demonstrate any consistent effect of bilateral topectomy on gastric secretion within five weeks after surgery. The gastric stimulants used were the gruel meal, insulin hypoglycemia and the epinephrine test.

Thus it would appear that, in both humans and animals, prefrontal lobotomy results in increased gastric acidity and increased gastric motility. In cats and dogs, at least, there is additional evidence that these phenomena are accompanied by increased gastric tonus and by engorgement of the mucosa. This triad of hyperacidity, hypermotility and erythema of the mucosa was observed by Wolf and Wolff [12] whenever Tom's stomach was in a secretory phase. These are the factors which are considered conducive to ulcer formation, and it is perhaps not surprising that peptic ulceration can occur following lobotomy.

Aside from this case and that of Sweet, there is no evidence that peptic ulceration occurs in humans after lobotomy. In none of the eight patients studied by the Columbia-Greystone Associates were any defects noted in the barium motility

study after lobotomy. It is true that their study was done within a month after surgery, while our patient apparently did not develop his ulcer until eight to 10 months after his operation. That the complication of ulcer is probably rare is also to be suspected from the fact that in the large series of lobotomies reported in the literature we have found no mention of postoperative symptoms suggesting an ulcer syndrome.

There are several possibilities in our case. The ulcer may have been purely fortuitous and have had no relation to the brain operation. It may have represented the recurrence of a previously healed gastric ulcer. The ulcer, on the other hand, and its sluggish response to healing, may have been due to the influence of the lobotomy in causing hypersecretion, hypermotility and hyperacidity. Thus the stage was set for ulceration at the time when the individual's dependent needs, formerly satisfied by psychotic devices, were threatened by attempted return to a less psychotic, more realistic and consequently more demanding life program.

Summary

A case is presented of a man who was discovered to have a chronic nonhealing gastric ulcer 10 months after bilateral frontal lobotomy.

A review of the literature reveals general agreement that ablation of the frontal cortex will result in increased gastric acidity and motility for an undetermined time after operation.

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SARCOIDOSIS ASSOCIATED WITH POLYARTHRITIS *

By MARTIN W. DAVIS, M.D., and RICHARD Q. CROTTY, M.D., *St. Louis, Missouri*

REPORTS of individual cases and series of cases of sarcoidosis have been increasing in the world literature in recent years.[1] However, its association with a polyarthritis has rarely been reported. Castellanos [2] reported this combination in a six year old Cuban boy, the arthritis resembling Still's disease. His patient died of generalized tuberculosis, and it is difficult to be sure how many of the manifestations may have been due to tuberculous infection. Zweifel [3] reported the combination in a Swiss girl 10 years old. In his patient, the joint involvement was due to an extension of the sarcoidosis from neighboring bones to the joints. Moyer and Ackerman [4] have recently reported two cases in which the sarcoid process extended to the joints. Moreau [5] has reported two cases of arthralgia in acute sarcoidosis. One of his cases had synovitis of the thumb, the other had hydrarthrosis of the knees. Scattered reports in the world literature have mentioned sarcoid involvement of joints without citing specific cases. Leitner [6] mentions a report by Ramel in which there was a coxitis later thought to be tuberculous. Kissmeyer [7] referred to articles by Schmidt, Lenz and Mayer in which joint involvement was described. Likewise Martenstein [8] reported a case of tenosynovitis with sarcoidosis. Most authorities state that arthritis associated with sarcoidosis does not exist except as a complication of severe sarcoid bone involvement. Michelson [9] stated that he has never seen a case of sarcoid arthritis in his extensive experience with sarcoidosis. Hench [10] has never encountered sarcoidosis in a patient with rheumatoid arthritis.

CASE REPORT

A 24 year old white female of Italian extraction was admitted to the hospital on July 1, 1949, with complaints of an arthritis of about two years' duration accompanied by an eruption on the face and forehead of 18 months' duration. She also showed evidence of a toxemia of several weeks' duration, with complaints of malaise, fever and recent weight loss.

The illness began as a mild arthritis, with pain on motion and swelling of the joints of the fingers and elbows. There was little change in this condition until she noted the appearance of an eruption on the forehead six months later; this was accompanied by a severe exacerbation of the joint symptoms. In a few weeks there was a spread of the joint symptoms to most of the large joints of all four extremities. At the same time the skin condition progressed with the development of other plaques on the forehead and face. A few weeks before admission the patient noted general malaise, fever and some weight loss. The past history revealed no rheumatic, cardiac or skin diseases. An injury to her spine as a child had left her with a permanent dorsal kyphosis. The patient's uncle had died from tuberculosis.

Physical examination revealed a fairly well nourished young woman, weighing 105 pounds and measuring five feet one inch in height. She had a temperature of 100° F. and appeared moderately toxic. There were obvious deformities of the elbows and ankles, with irregular swelling and limitation of motion but no erythema. There were only minimal changes in the wrists. The hands were involved principally at

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Studies, observations and reports from The Barnard Free Skin and Cancer Hospital.

the metacarpophalangeal and proximal interphalangeal joints. The characteristic spindle-shaped deformity of rheumatoid arthritis was not observed, the swelling being more irregular and variable. The skin lesions consisted of two large brownish plaques on the forehead and three other smaller lesions on the left side of the face. The lesions were definitely infiltrated and demonstrated some follicular plugging on their surfaces. All of the lesions were well circumscribed (figure 1). There was a coarse systolic murmur at the apex of the heart, with no presystolic phase or thrill. The heart was not enlarged. The remainder of the examination was essentially negative, except for a moderate kyphosis of the thoracic spine.

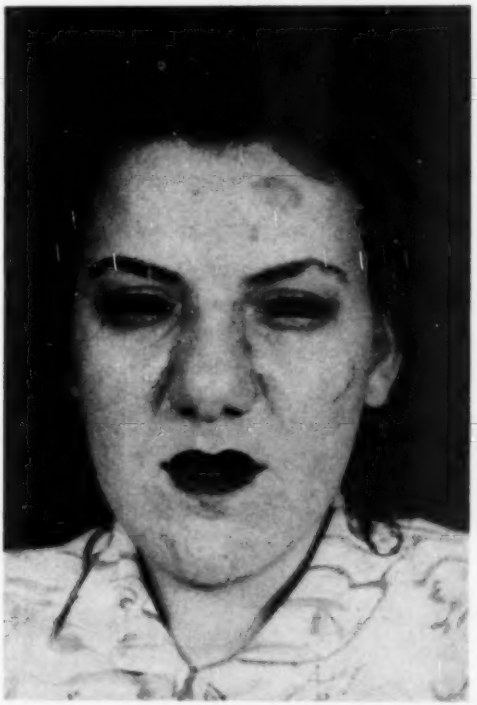

FIG. 1. Photograph of patient made July 1, 1949, showing sarcoid plaques on face.

Laboratory examination revealed normal blood counts except for a mild hypochromic anemia. Urinalysis was negative. The sedimentation rate, using the Wintrobe method, was elevated to 52 mm./hr. The total serum protein was 8.85 gm. per 100 c.c.; the serum albumin was 3.6 gm. per 100 c.c., and the serum globulin was 5.25 gm. per 100 c.c. Tuberculin tests were negative, using 0.00002 mg. and 0.0005 mg. of purified protein derivative. A sternal bone marrow aspiration revealed a normal cellular picture. A biopsy was performed on one of the plaques on the forehead. Dr. John B. Frerichs, pathologist at the Barnard Hospital, reported:

"Extending over a long zone of the slide and ranging in depth from the level of the sebaceous glands or slightly below, to almost immediately beneath the epidermis, there are large numbers of sometimes confluent practically pure naked tubercles associated with only a minimum of non-specific mononuclear cell infiltration and this is

FIG. 2. Photomicrograph of section showing sarcoid changes in skin (H & E, × 150).

situated focally rather than diffusely. Good Langhans' type giant cells and epithelioid cells make up the bodies of the lesion and there appears to be some fibroblastic activity also (figure 2). No necrosis is seen. Reasonably complete search at this time fails to find either Schaumann or asteroid inclusion bodies."

Roentgenograms were taken of the chest, small bones of the hands and feet, elbows, wrists, skull and spine. The roentgenograms of the hands and feet revealed only minimal cystic changes of the type described by Jüngling.[11] The diffuse rarefaction type of bone involvement described by Reisner[12] was not observed. Dr. George K. Henshall, radiologist at the Barnard Hospital, reported:

Chest (June 13, 1949): "There is no significant widening of the upper mediastinal shadow. The mid-mediastinum is widened at the level of the arch of the aorta due primarily to paravertebral changes between the sixth and eighth dorsal vertebrae. The aorta and cardiac shadows are essentially normal in size, position and con-

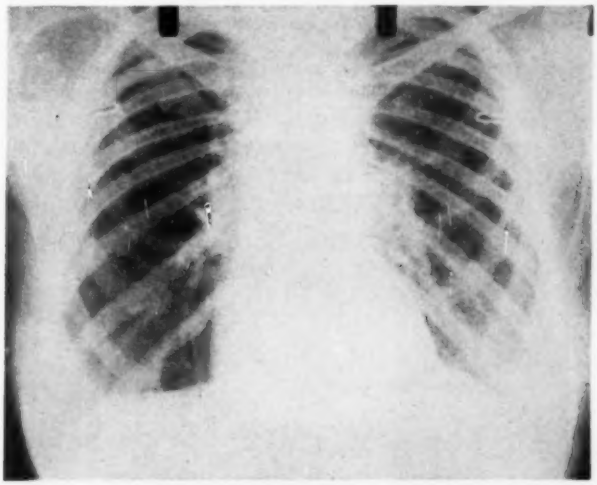

FIG. 3. Roentgenogram of chest made June 13, 1949, showing changes indicative of sarcoid.

figuration. The diaphragms are smooth, the costophrenic sinuses are clear. The hilar and perihilar areas are thickened. There is discrete bilateral nodal adenopathy in both hila. There is strand-like thickening of the interstices of the lung structures with some nodular infiltrations of varying size in the mid zones of both lung fields. The peripheral zones are essentially clear." (Figure 3.)

Chest (January 30, 1950): "Minimal resolution of the nodal adenopathy in the hila and very minimal clearing in the mid zones of both lung fields."

Left Foot: "On the medial aspect of the head of the proximal phalanx for the left great toe, there is a small subcortical cystic area, which appears to have actually ruptured the cortex. Similar changes occur in the head of the fifth left metatarsal on the lateral aspect, except that the cystic changes have only produced thinning of the adjacent cortex."

Elbows: "Examination of both elbows reveals suggestive thinning of all joint spaces. No osteoarthritic changes are demonstrated, and no associated osteoporosis

is noted. There is an area of roughening on the radial articular surface of the left humerus. The changes are minimal but may be of clinical significance." (Figure 4.)

While in the hospital, the patient developed a firm subcutaneous nodule near the left elbow. It was excised and the microscopic examination revealed that it was a rheumatic nodule with no evidence of sarcoidosis. Dr. Frerichs reported:

"There are zones of collagen denaturation in which the tissue is intensely edematous and the normal fibrillary pattern of the collagen is subtotally to completely lost. These zones show trivial infiltration by mononuclear inflammatory cells including plasma and some epithelioid cells. These zones are rimmed about by foci of inflammatory cell infiltration in which epithelioid forms are common and even a few giant cells are seen. The most characteristic appearance present is that of pallisading of the cells immediately adjacent to the necrotic collagen central foci. Here the cells are arranged with a definite long axis and this long axis is perpendicular to the overall fringe border which they make up." (Figure 5.)

During the patient's stay in the hospital, therapy consisted of bed rest, salicylates, a high vitamin diet and calciferol. After about one month her general condition improved, with a return of her temperature to normal, a gradual lowering of the sedimentation rate to 15 mm./hr., and subsidence of some of the pain and swelling in the

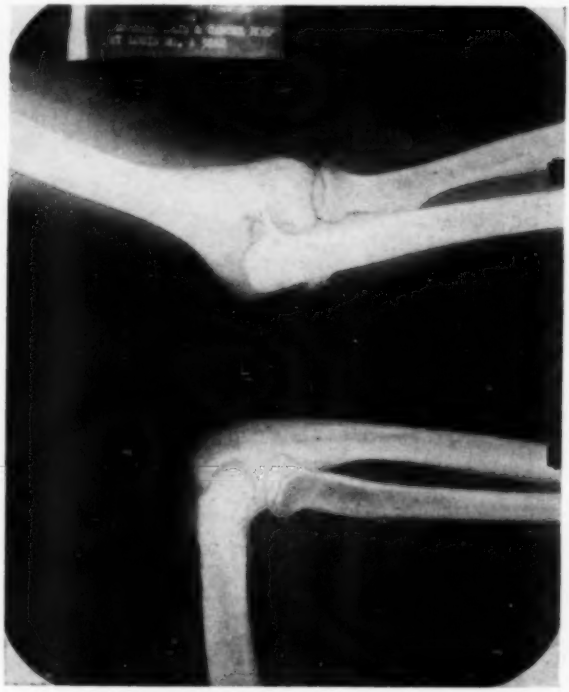

FIG. 4. Roentgenogram of left elbow made December, 1949.

FIG. 5. Photomicrograph of section of rheumatic nodule from left elbow (H & E, ×150).

joints. Since discharge from the hospital she has been given 13 weekly injections of gold sodium thiosulfate, 20 mg. each, with no change in her condition. Physiotherapy was instituted with only questionable help. She has been given streptococcus vaccine in gradually increasing doses, with no improvement. She was given a course

of glucuronic acid therapy with no benefit. Repeated blood counts and urinalyses have given essentially normal results. The tuberculin tests were repeated in December, 1949, and the second strength P.P.D. gave a 2 plus reaction. Total serum proteins in January, 1950, were 8.85 gm. per 100 c.c., albumin 4.90 gm. per 100 c.c., and globulin 3.95 gm. per 100 c.c.

Discussion

This woman fulfills the diagnostic criteria for generalized sarcoidosis and a rheumatoid type of arthritis. Sarcoidosis is manifested by the typical skin lesions with a sarcoid picture on biopsy, pulmonary infiltration and hilar adenopathy seen on the roentgen-ray, small cystic areas in some of the bones of the feet, and elevation of the serum proteins with reversal of the normal albumin/globulin ratio. The arthritis is manifested by subjective and objective changes in the joints, including swelling, tenderness and limitation of motion. Roentgenograms of the joints show narrowing of the joint space and some roughening of the articular surfaces. The bones adjacent to the involved joints do not show the cystic changes of sarcoidosis, and involvement of the bone marrow by sarcoidosis was not demonstrated by aspiration biopsy of the sternum. The juxta-articular nodule which was biopsied showed the microscopic picture of a rheumatic nodule. The patient did have at one time a mild toxemia with a low grade fever, elevated sedimentation rate and a hypochromic anemia. There is a persistent coarse systolic murmur at the apex.

Arthritis might conceivably arise in conjunction with sarcoidosis by at least five different mechanisms: as an extension to the joint from sarcoid involvement of the bones; as a primary involvement of the synovia by a sarcoid process; as part of the general toxemia of the sarcoidosis; as a separate condition but caused by the same etiologic agent as the sarcoid; or as an entirely unrelated condition. The two cases of Moyer and Ackerman [4] were definitely an extension of the sarcoid process from neighboring bones to the joint space. Roentgenograms of the bones showed the diffuse rarefaction type of bony involvement seen in sarcoidosis, with rupture into the joint spaces. The case of Zweifel [3] also was an extension from a diffuse process in neighboring bones. Roentgenograms showed diffuse rarefaction, and a bone marrow biopsy showed sarcoidosis. Because of other features in his case, Zweifel felt that the arthritis was a manifestation of Sjögren's syndrome. This syndrome, first described in 1933,[13] is more frequently seen in Europe than in the United States, where only one case has been reported. The syndrome is characterized by a loss of secretion of the lacrimal and salivary glands, dryness of the mucous membranes, and frequently a polyarthritis. Zweifel does not believe there is any relationship of Sjögren's syndrome to sarcoidosis, although it may superficially resemble the uveoparotid fever syndrome sometimes seen in sarcoidosis.[14]

The case of Castellanos [2] is harder to explain. The large joints of the extremities were principally involved and showed considerable serous effusion, resembling Still's disease. His case terminated with generalized tuberculosis, and it is impossible to say whether the arthritis was related to the sarcoidosis, to the toxemia of the tuberculosis, or was an independent complication. His case resembles our patient in many features but had a more severe arthritis. Our patient never developed effusion into the joints and has not manifested any symptoms of tuberculous infection.

Moreau has reported two cases of acute sarcoidosis with toxemia and generalized arthralgia. The two cases had fevers of 39° and 40° C., respectively. One of his patients had a marked arterial hypotension and leukocytosis. In one case there was a synovitis of the thumb. In the other case there was a hydrarthrosis of both knees, which lasted only three days and was relieved by salicylates. His cases both recovered, with no evidence of chronic arthritis. They probably represent an example of a fleeting arthritis arising as part of the general toxemia of sarcoidosis. He does not describe the roentgen-ray appearance of the joints, and a more definite analysis of his cases is not possible from the data he presents.

The most likely explanation of our case is that two separate diseases occurred more or less simultaneously in the same individual. Her arthritis did get much worse when the skin lesions appeared, but we believe that her sarcoidosis caused an exacerbation of her arthritis, just as most infections will cause a flareup of arthritis. The joint symptoms did precede the skin involvement by six months. This would make it appear that the sarcoidosis could not have caused the arthritis, although it is possible that the systemic sarcoidosis preceded the skin manifestations. Her arthritis almost certainly was not due to an extension from bony lesions. We were denied permission to do a synovial membrane biopsy, which might have given a definite answer as to the type of joint involvement.

A variety of therapeutic agents has been recommended for both these conditions, with questionable value in both instances. The consensus now is that the outlook in sarcoidosis is good, that no known agents are of any proved value, and that consequently the therapy should be supportive and symptomatic. Sarcoidosis probably is an altered type of reaction, possibly to several different agents,[1] and this consideration influenced us in a decision to avoid the use of foreign protein therapy for the arthritis. We did give her a course of gold sodium thiosulfate, 13 injections intravenously of 20 mg. each, at weekly intervals. She showed no improvement on this therapy. We have given her physiotherapy, which has maintained reasonably good motion in all the joints except the elbows. The left elbow now shows about a 30 per cent limitation of flexion and extension. We have given her injections of streptococcus vaccine and tablets of glucuronic acid without noticeable benefit. She is now improving slowly with salicylates and supportive therapy: iron, multiple vitamins and rest.

Summary

1. We have presented a case of sarcoidosis with polyarthritis. We have been able to find only four other cases in the literature. All of these cases differed from our case in many respects.

2. The arthritis in our case resembled a rheumatoid arthritis, but did not improve with gold therapy. We felt that the two conditions were separate entities occurring simultaneously. It is remarkable that no one has reported such a coincidence before.

Acknowledgment

The authors are greatly indebted to Dr. Henry E. Michelson, of Minneapolis, Minnesota, for helpful suggestions and contributions to the bibliography.

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IDIOPATHIC ACQUIRED HEMOLYTIC ANEMIA TREATED BY ACTH AND CORTISONE*

By HORACE I. CRARY and IRVING A. BECK, *Providence, Rhode Island*

ACQUIRED hemolytic anemia is a rare and chronic disease often accompanied by severe hemolytic crises. The red cell injury appears directly related to erythrocyte bound antibodies [1] which may be detected by the Coombs' test.[2] Numerous investigations have indicated that antibodies are produced by lymphocytes [3] and possibly by the reticuloendothelial system.[4] Attempts to destroy lymphoid tissue, and therefore the source of these injurious antibodies, by x-ray, nitrogen mustard and urethane, or to inhibit the reticuloendothelial system by Congo red saturation, have been of limited value.[5] Splenectomy, which removes the largest lymphoid and reticuloendothelial organ in the body, has been of benefit in some cases, but it has a high mortality during a hemolytic crisis. ACTH and cortisone have been shown to cause regression of lymphoid tissue in lymphomas [6] and to alter favorably the pathologic sequelae of numerous allergic states.[7] It is therefore not surprising that improvement has occurred in the few cases of idiopathic and symptomatic acquired hemolytic anemia in which these hormones have

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From the private Medical Service of the Rhode Island Hospital.

recently been tried.[6, 8, 9, 10, 11] The purpose of this paper is to present an additional case with some unusual features and continuing therapy.

Case Report

A 63 year old white married woman was admitted to the Jane Brown Memorial Hospital on February 17, 1951. She was first seen by her family physician in March, 1922, with a history of dyspnea, ankle edema, palpitation and jaundice for two weeks. At that time there were found evidence of mitral stenosis, a systolic aortic murmur, a spleen felt below the level of the umbilicus, ankle edema, a temperature of 101.8° F., moderate jaundice, a white blood count of 3,200, a red blood count of 2.60 million, hemoglobin 50 per cent, and a red cell fragility test showing hemolysis beginning in 0.46 per cent saline and complete in 0.36 per cent saline. Her urine was negative for bile and hemoglobin, but urobilinogen appeared increased. She was observed to become less jaundiced and to have regression in the size of her spleen until January, 1923, when the spleen was no longer palpable. A blood count in September, 1923, revealed a white blood count of 5,400 and red blood count of 4.80 million; her hemoglobin was 80 per cent. She next came under recorded medical attention in 1938, when her family physician saw her for biliary colic and jaundice. She was admitted to this hospital in 1939 with obstructive jaundice. At that time an abdominal x-ray revealed multiple calculi in the hepatic duct, common duct and gall-bladder. Surgery was advised but the patient refused. Her red blood count, hemoglobin and red cell fragility tests were normal. In 1949 she again had colicky abdominal pain and jaundice. In 1950, one year before admission, she noted weakness and dyspnea on exertion, and was told that she was anemic. Oral iron did not correct her anemia and her weakness, and dyspnea and substernal distress on exertion progressively increased to a point where she was confined to bed for one week prior to admission.

Physical Examination: The patient was an extremely pale, dyspneic woman who was fatigued by the examination. The skin was cool and moist and had an icteric tinge, as did her sclerae. Pulse rate was 80 per minute; systolic pressure was 120 mm.; diastolic pressure was not obtained because the sounds did not change their intensity with release of cuff pressure. Temperature was 98° F. Eye ground examination showed a small white area above the left optic disc and two small hemorrhages below it. Her tongue was coated and had normal distribution of papillae. Lungs: Few crackles at extreme right base. Heart: Percussed 3 cm. to the left of the midclavicular line. A grade II rough systolic murmur was heard at the apex. The liver could not be palpated. Rectal: No abnormality noted. Reflexes: Biceps jerks active bilaterally; knee jerks and ankle jerks not elicited. Babinski equivocal because of withdrawal response.

Laboratory: Hematocrit, 13.3 per cent; red blood cells, 1.09 million; hemoglobin, 3.9 gm.; white blood cells, 9,150; polymorphonuclears, 85 per cent; lymphocytes, 14 per cent; basophils, 1 per cent; two nucleated red blood cells per 100 white blood cells. Platelet count, 90,000. Reticulocyte count, 1.7 per cent. Urine: mahogany colored, but negative for bile; specific gravity, 1.018; protein, trace; sugar, negative; microscopic: 100 white blood cells per high power field. Blood urea nitrogen, 39 mg. per cent. Glucose, 92 mg. per cent. Total serum protein, 7.2 gm. per cent; albumin, 5.0 gm. per cent. Thymol turbidity, 16 u. Alkaline phosphatase, 2.1 King Armstrong units. Prothrombin activity, 90 per cent of normal. Hinton, negative. Cold agglutination, positive, 1:16 dilution. Bleeding time, two and one-half minutes. Clotting time, 13.5 minutes. Tourniquet test for petechiae, negative. Red blood cell fragility, 0.44 to 0.22. Stool guaiac, negative. Coombs' test, positive. Examination for warm, cold and acid hemolysis produced only slight hemolysis under all

conditions. Urinary urobilinogen, 0.8 mg. per cent. Total serum bilirubin, 4.8 mg. per cent. Direct serum bilirubin, 1.1 mg. per cent.

Course: With an incomplete and inaccurate history on admission the diagnosis was not clear, but as additional data were obtained it became evident that we were dealing with the hemolytic crisis of an idiopathic acquired hemolytic anemia. When the blood count improved, a diastolic apical murmur, consistent with mitral stenosis, became audible. On the patient's third hospital day a consultant noted frequent spherocytes in her blood smear, and regarded the low platelet count (90,000) as a possible result of hypersplenism. He considered the picture consistent with ac-

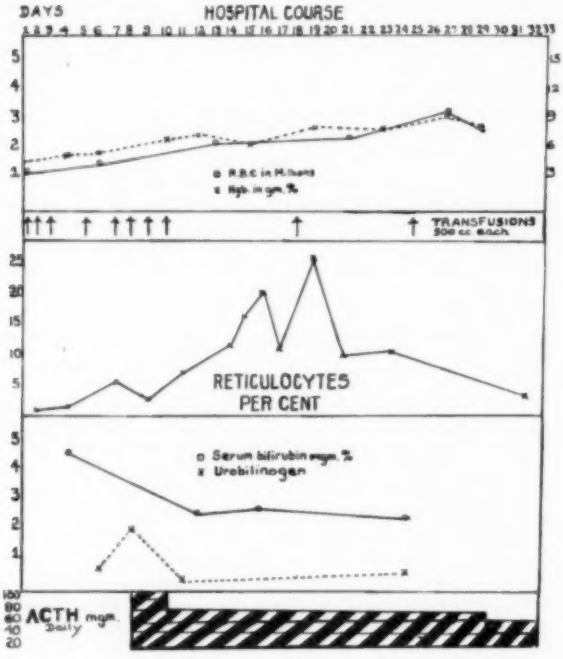

FIG. 1.

quired hemolytic anemia and advised against splenectomy at this time. Although she received six transfusions during the first eight days, there was no attendant rise in her red cell and hemoglobin values. Her jaundice increased and her urinary urobilinogen rose, but her reticulocytes reached a high of only 5.7 per cent. On her seventh hospital day she was almost moribund; she became extremely dyspneic and developed fine basal râles after 500 c.c. of blood, followed by 400 c.c. of saline, were given intravenously. In addition to the transfusions, she was given ferrous sulfate, 0.2 gm. three times daily from the third to the eighth day, and vitamin B_{12}, 30 micrograms on the sixth through the eighth hospital day. On her eighth hospital day her condition was, if anything, worse. She was febrile and dyspneic, and complained

of substernal distress on the slightest exertion. Her systolic blood pressure was 130 mm. Hg, and her diastolic pressure was still not obtainable. Frequent ventricular premature contractions were present, a patch of moist râles was audible over the left lower lobe, and her spleen had descended to 6 cm. below the left costal margin.

At this time ACTH therapy was begun, in a dosage of 25 mg. intramuscularly every six hours for two days, and was then reduced to 15 mg. every six hours. After 48 hours of ACTH therapy the patient was subjectively improved, and her hemoglobin had risen from 5.8 gm. to 7.5 gm. After 72 hours of ACTH, her temperature fell to normal and has remained so since. As noted in figure 1, she was continued on ACTH until her thirty-first hospital day, when the dosage was reduced from 15 mg. to 10 mg. every six hours. Her clinical condition continued to improve. Her hemoglobin, red blood count and reticulocyte count rose, the latter to a maximum of 26.4 per cent, and her serum bilirubin and urinary urobilinogen fell.

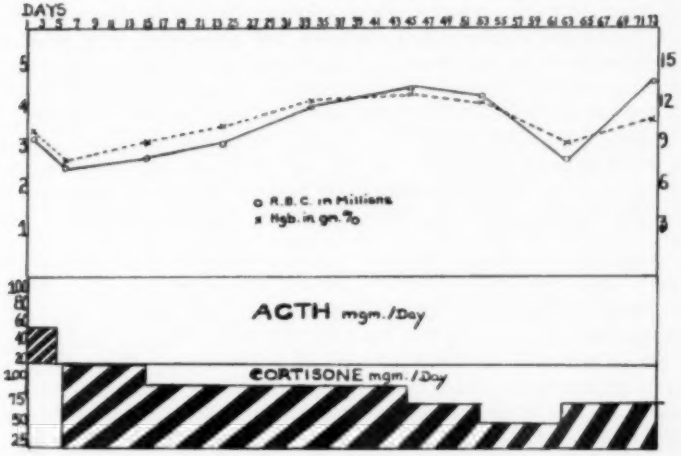

FIG. 2. Course at home following hospital discharge.

She was discharged on March 30, her thirty-second hospital day, to be continued on ACTH at home. Her discharge diagnoses were: acquired idiopathic hemolytic anemia; rheumatic heart disease, inactive, with mitral stenosis; biliary tract lithiasis, and possible biliary cirrhosis.

After the patient had been at home for six days, treatment was changed to oral cortisone, 100 mg. daily (figure 2). This was reduced to 75 mg. daily on her fifteenth day at home, 50 mg. daily on the forty-fifth, and 25 mg. daily on the fifty-third day following hospital discharge. During this period her hemoglobin had gradually risen to 12.6 gm. Ankle edema disappeared, the spleen receded to 2 to 3 cm. below the left costal margin, her blood pressure rose to 150/70 mm. of Hg, and the patient stated that she felt better than she had for years. As noted in figure 2, when the cortisone dosage was decreased to 25 mg. daily the hemoglobin dropped in 10 days to 9.2 gm., with a red blood count of 2.69 million. Because of this hematologic relapse, the cortisone was increased to 50 mg. daily, and her hemoglobin and red cell values rose.

Discussion

This elderly patient had maintained a fairly healthy life in spite of a known history of acquired hemolytic anemia for 29 years. Numerous biliary calculi had formed, but for two years prior to this admission had not produced biliary colic. With her most recent hemolytic crisis, however, she became critically ill. Characteristically, hemolysis of transfused red cells was so rapid that she remained in severe anoxia.[12, 13] She was considered a poor risk for splenectomy, an operation of unpredictable value in this disease.[10] Her rheumatic heart with its limited cardiac reserve, as evidenced by an episode of pulmonary edema, angina decubitus and peripheral edema, made transfusions hazardous. No evidence was found of lymphoid or reticuloendothelial proliferative disease, a relatively frequent cause of acquired hemolytic anemia,[14] nor would such evidence be expected from the known duration of her disease. Within 48 hours of ACTH therapy her clinical condition had improved, and there were both decrease in hemolysis and increase in red cell production, reflected by serum bilirubin, red blood count, hemoglobin and reticulocyte values. Improvement of her hemoglobin and red cell values with ACTH, and later oral cortisone treatment, was progressive, and her spleen regressed in size. A hematologic relapse occurred when her daily cortisone dosage was reduced to 25 mg., but improvement followed rapidly when her daily cortisone was increased to 50 mg. In spite of her poor cardiac reserve, no serious degree of fluid retention was observed.

Summary and Conclusions

1. A case of idiopathic acquired hemolytic anemia of 29 years' known duration, complicated by long standing rheumatic heart disease, biliary lithiasis and possible biliary cirrhosis, developed a severe hemolytic crisis. With ACTH and cortisone treatment, an almost complete remission of the hemolytic process was obtained. At this writing, four months after the onset of therapy, the patient is being maintained in remission on 50 mg. of cortisone daily.

2. ACTH or cortisone appears to be the treatment of choice for acquired hemolytic anemia in crisis.

Addendum

Since the above paper was submitted for publication, the patient's course has been as follows.

As previously described, her hemoglobin and red blood count values rose when cortisone was increased from 25 mg. to 50 mg. daily. Seven months after the hospital discharge, her hemoglobin had dropped to 8 gm. Cortisone dosage was therefore increased to 75 mg. daily. Two months later, her hemoglobin was 7.8 gm. and the Coombs' test negative. It appeared that hemolysis was controlled less effectively than previously with cortisone, and the dosage was increased to 100 mg. daily. On January 13, 1952, ten months after discharge, she was hospitalized with bronchopneumonia and cardiac decompensation. Icterus and splenomegaly were present. Laboratory reports included Hgb. 7.2 gm., R.B.C. 2.36 million, W.B.C. 9,000 which rose to 40,050, positive Coombs' test, bilirubin 2.3 mg. per cent, reticulocyte count 16.7 per cent which fell to 1.6 per cent. Successive trials with aureomycin, penicillin, chloromycetin, and streptomycin were ineffective in lessening her fever or signs of pneumonia. It was considered that the cortisone therapy might have interfered with the patient's antibody defense against the pneumonia. On the patient's twentieth hospital day, over 11 months after starting ACTH therapy, she died. Necropsy permission was not obtained.

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ACUTE PORPHYRIA WITH IMPROVEMENT DURING AND FOLLOWING PREGNANCY *

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ACUTE porphyria is a disease characterized by one or more of the following symptoms: intense abdominal pain, diffuse muscular aching, peripheral neuropathy, psychic disturbances and discoloration of the urine ranging from pink to purple. It differs from congenital porphyria in that the acute type frequently affects adult women, whereas the congenital type affects young boys preponderantly. Moreover, in congenital porphyria, vesicular skin lesions aggravated by exposure to ultraviolet radiation are characteristic, while the acute type has no

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skin manifestations whatever. Both are thought to be inheritable diseases, although the literature is not altogether convincing on this point. In both types of porphyria there is increased excretion of coproporphyrin and uroporphyrin in both urine and stool.

The porphyrin nucleus is a normal constituent of hemoglobin and of chlorophyll in plants. It is thought that normally excreted porphyrin is derived from food ingested; whether the increased excretion of porphyrins in porphyria is due to a failure to metabolize that which is normally ingested, or whether it is due to a metabolic fault, remains in doubt. Apparently the quantities of these materials excreted in porphyria do not fluctuate in proportion to the intensity of the patient's symptoms.

Acute porphyria is normally diagnosed when characteristic symptoms are present and the urine is simultaneously discolored. During remissions it is possible for the urine to be red, though the patient is otherwise symptom free. Conversely, in the presence of suggestive symptoms, such as intense abdominal pain without rigidity, even though the urine be normally colored, porphyria may be recognized by the identification of urinary porphobilinogen, according to the method of Watson and Schwartz.[1]

Two patients with porphyria who became pregnant and were successfully delivered have been reported. The first of these was a case of congenital porphyria with vesicle formation, described by Linas et al.,[2] in which the patient suffered an exacerbation of the cutaneous lesions during most of her pregnancy but improved following delivery and was well when seen at intervals up to six months after delivery, despite the continued excretion of increased amounts of porphyrins during the puerperium. In the second case, one of acute porphyria reported by Coleman,[3] the patient became aware of symptoms during the second week of pregnancy, although orange colored urine had been noted for several years previously. She was critically ill during the early part of the first trimester, but during the second and third trimesters progressed normally and was delivered of a normal child by section. She was symptom-free nine months after delivery, although urinary discoloration continued to be present.

The present case is the third to be reported of porphyria in which pregnancy occurred. In this patient following 10 months of severe illness there occurred a brief period of remission. During this remission the patient became pregnant. Following the onset of pregnancy, exacerbation occurred in the first trimester, but during the second and third trimesters the patient recovered clinically to a remarkable degree, delivered a normal child and now, almost two years after delivery, continues to be well despite occasional excretion of discolored urine.

Case Report

A 24 year old white married female, para 3 gravida 3, became aware of red urine, dysuria and frequency in December, 1945. On June 9, 1946, she first noted jerking spells without loss of consciousness, fever for several days, and marked weakness of all her extremities. She was hospitalized near her home three weeks later, at which time she was rigid and had clonic movements, generalized muscle pain, nausea and vomiting, and pain in the lower abdomen radiating from the spine through to the suprapubic area. During this period there was fever of unknown degree, headache, stiffness of the neck, and stool and urinary incontinence. There was no

history of a skin eruption or delirium. She was transferred to the North Carolina Baptist Hospital of the Bowman Gray School of Medicine on July 20, 1946.

The patient had always been well. There was no family history of skin eruption or urinary discoloration. Her home was in an isolated community, and her husband farmed a small plot of poor land. No history of drug habituation or of the use of sedatives could be obtained.

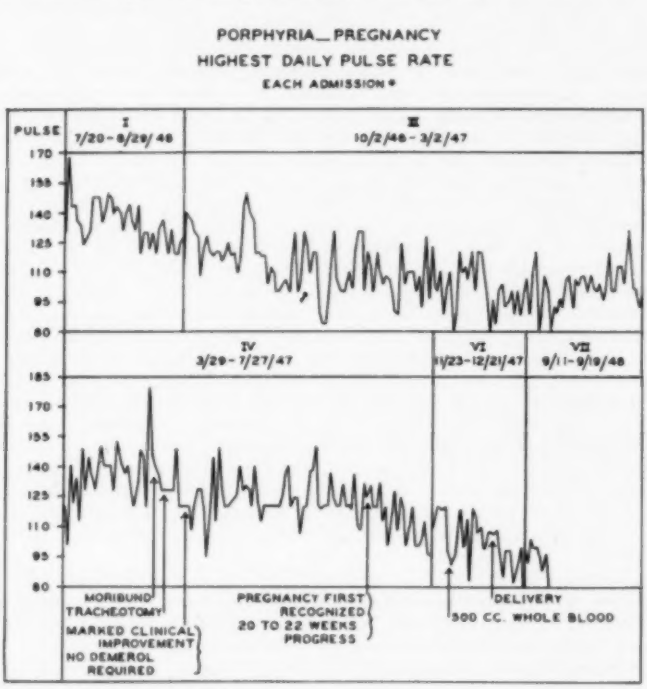
Physical Examination: Blood pressure, 108 mm. Hg systolic and 70 mm. diastolic; pulse, 120; respiration, 18; temperature, 101.6° F. The patient was critically ill and unable to speak above a whisper. There was marked emaciation. She was flushed but entirely rational. There was slight meningismus, with a questionably positive Brudzinski sign. There was no lymphadenopathy. The pupils were of equal size and reacted. Extraocular movements were normal. There was no nystagmus. Except for questionable dilatation of the retinal veins, the fundi were negative. Hearing was equal bilaterally. The tongue was in the midline. The teeth were markedly carious but not discolored, and gingivitis was extensive. The gag reflex was absent. Singultus was present. The thyroid gland seemed to be diffusely enlarged. The thorax was symmetrical, and costal breathing of the Cheyne-Stokes type was strikingly present. The lungs, however, were clear, with no râles and no dullness. The heart sounds and size were both normal, with a regular rhythm and no murmur, but the rate was extremely rapid. The patient's color was good. Protruding abdominal distention was apparent between the xiphoid and the umbilicus, symmetrically placed in the midline. No peristaltic sounds were heard, and no masses were made out other than that of the localized distention. Both costovertebral angles were quite tender. The vaginal outlet was parous; the uterus and adnexae were negative. The rectal tone was good, and brown stool was obtained on the examining finger. All extremities could be moved, although very feebly, and a suggestion of wrist-drop was present bilaterally. No reflexes could be obtained. There was some question as to the patient's perception of the various modalities of sensation, in her subdued level of consciousness, but it was believed that these were present normally, except for absence of position sense. Straight leg-raising elicited evidence of pain, with marked grimacing of the face and retraction of the upper lip. No sucking or grasping reflex was present. Rotation of the shoulders produced flexion of the opposite thigh and leg.

Aspiration of the stomach was performed, 500 c.c. of greenish watery fluid were removed and the distention promptly disappeared, but there were still no peristaltic sounds audible. The patient voided involuntarily in bed shortly after her admission, and it was noted that the urine stained the bedclothes bright red.

Course in Hospital: Singultus persisted for several days; Demerol was administered for the relief of pain, and the patient was hydrated. On the fifth hospital day she was able to eat but did not voluntarily move her left arm. Her voice became stronger, but her complaints of pain did not diminish. She was still not clear mentally on the eighth hospital day, and fibrillary twitching of the mouth, face and right leg was noted. The neck was supple. The urine at this time was no longer bright red but muddy pink in color. On subsequent days she became better oriented, but illusory thinking persisted. Ptosis of the lids was apparent. The proximal limb muscles became stronger and could be moved if the limb was supported; the gag reflex returned and the tremor became less, but the reflexes did not return. There were marked sweating around the mouth and diminished sensation to pinprick over the entire body. Peristaltic activity returned on the ninth hospital day. On the thirteenth hospital day her general muscular activity improved, and she became able to move some of the smaller muscles of her hands. The facial sweating persisted. All of the symptoms and signs previously mentioned continued to greater or less degree through the thirtieth hospital day. She was discharged on the thirty-eighth

day, August 29, 1946, with most of her symptoms improved and with much less pain, but with evident foot-drop and wrist-drop and with no reflex responses, deep or superficial.

The pulse rate reached 130 almost every day, often rose as high as 140, and on a few occasions was up to 160 (chart 1). The temperature was usually up to 100° F. daily, and occasionally to 101° F. Respirations fluctuated from 12 to 36 per minute. The blood pressure varied from 110/80 to 150/100.



* Indicated by Roman numerals.

CHART 1.

Among the medications administered were iodides, neostigmine, potassium citrate, coramine, paraldehyde, liver, vitamins, including methionine, and iron—none of which was felt to be effectual in altering the patient's symptoms.

Laboratory examinations revealed the following:

Urine: The color varied from reddish black to pink, and tests for porphobilinogen were consistently positive. The reaction was acid, the specific gravity was within normal range, and neither albumin nor sugar was found. Occasional red cells were seen, but the benzidine test was consistently negative for occult blood. White cells were usually few, but on one occasion 15 per high power field, centrifuged, were observed. Rare granular casts were present in all specimens. On culture, *Escherichia coli, Streptococcus fecalis* and *Aerobacter aerogenes* were found.

Blood: The hemoglobin remained around 11.0 gm., with from 3.5 to 4.0 million red blood cells present. White blood cells ranged from 6,000 to 11,000, with 92 per cent polymorphonuclears on admission, dropping later to 74 per cent, all segmented. There were no eosinophils. Serologic test for syphilis was negative.

Blood Chemistry: Non-protein nitrogen on admission was 115 mg. per 100 c.c., but this gradually returned to normal with hydration. CO_2 combining power was initially 86 vol. per cent (probably due to loss of HCl from persistent vomiting), dropping later to normal levels. Chlorides were 248 mg. per 100 c.c., later restored to normal. Phosphorus was 2.9 mg. per 100 c.c.; calcium, 11.9, and alkaline phosphatase, 4.3 Bodansky units. Total serum protein varied from 5.2 to 8.8 gm. per 100 c.c., but the A/G ratio was normal. Bromsulfalein test on two occasions showed 40 per cent and 25 per cent retention of dye after 45 minutes. Prothrombin time was 16 seconds, the control being 14.8 seconds. Hippuric acid excretion test was reported as 0.21 gm. calculated as benzoic acid (normal, 0.68 gm.).

Cerebrospinal Fluid: On admission, protein was 55 gm. per 100 c.c., chlorides were 105.4 mEq., and 60 cells, type undescribed, were present. A second tap was negative eight days later.

Stool: Negative for blood and parasites.

Second Admission: The patient was re-admitted on September 8, 1946, because vomiting had begun again on the previous day. Her voice was stronger, and she was able to flex her legs but unable to extend them. Peristaltic activity was present but subdued; there was deep bone pain present. The thyroid gland was no longer enlarged. Reflexes were absent. A soft systolic murmur was present at the apex. Wrist-drop and foot-drop persisted. All sensations were normal. She was discharged after one week on September 15, 1946, having received iron, penthothal, aspirin and vitamins.

The pulse during this admission reached 120 to 130 daily, although this was not usually maintained during the 24 hour period. Temperature was usually over 99° F. at some time during the day.

Laboratory:

Urine: Red-brown in color; positive for porphobilinogen; specific gravity, 1.023; no albumin or sugar; 25 to 30 white blood cells per high power field centrifuged, with occasional white blood cell casts.

Blood: Hemoglobin, 9.5 gm.; red blood cells 3.9 million; white blood cells, 4,650; polymorphonuclears, 62 per cent; eosinophils, none.

Blood Chemistry: Non-protein nitrogen, 40 on admission, subsequently 34. Sugar, 86; CO_2, 49; chlorides, 560; cholesterol, 200. Total serum protein was 6.2 gm., with normal A/G ratio. Bromsulfalein test revealed 15 per cent retention after 45 minutes. The hippuric acid test revealed 0.18 gm. excreted, computed as benzoic acid.

On September 30, two weeks after discharge, when the patient was seen in the Out-patient Department she complained of occasional pain but was able to raise her arms over her head, had regained some strength, and was eating reasonably well. The urine was still red.

Third Admission: The patient was re-admitted on October 2, 1946, having had fever for two days, dysuria and pain in the suprapubic region. She had shortness of breath on turning in bed and precordial pain with radiation to the left arm, and still had foot and wrist drop. For the next three weeks she had persistent pain in various parts of the body: hips, thigh, neck and behind the eyes. She vomited at intervals, some of the vomitus containing bile, and she continued to have dysuria and costovertebral angle tenderness. Delirium was often apparent, but there were many lucid intervals. Demerol was administered in fairly large dosage for control of the

pain, with only moderate effect. On the twenty-fourth hospital day there was marked improvement, with increase in rationality and increase in appetite. It was thought, however, that the patient had acquired a Demerol addiction, and it appeared that she became nauseated when the drug was refused. Because of the marked gingivitis and the possibility that bacteremia from this source might be contributing to her urinary tract infection and perhaps to some of her other symptoms, she had dental extractions performed on the twenty-ninth hospital day, with good clotting and prompt healing of the surgical area. However, shortly after this procedure she lapsed back into complaint of frequent pain, nausea and vomiting, and reported paresthesia of the extremities. The muscle power seemed to be improved, but drowsiness was apparent, and there were diffuse vague pains in the chest, abdomen, thighs and back. Improvement in strength fluctuated, but was sufficiently good on the fiftieth hospital day to allow her to be in a chair. However, shortly after this she became worse again, and on the sixtieth day had chemosis and swelling of the face generally, and tenderness of the maxillary sinuses. On the eightieth hospital day it was possible to get her up again to walk with the aid of a mechanical device, but the pain in the extremities and in the abdomen persisted. On the hundredth hospital day she moved her toes and feet, and two weeks after that she suddenly seemed to feel quite well. During all this time she had been receiving Demerol, and had been given protein hydrolysate intravenously on alternate days to maintain her nutrition. Unless this was given extremely slowly, over a 10 hour interval for one liter, the patient invariably vomited. On the one hundred twelfth day her weight was recorded as 66 pounds (height, approximately 58 inches). She was finally discharged on March 2, 1947, after having been in the hospital five months, and was permitted to continue to take Demerol at home for relief of pain.

The pulse ranged from 110 to 150 daily. Temperature was over 99° F. at least once daily.

Medications consisted of Demerol, from 50 to 400 mg. daily, other opiates in varying dosage, placebos, atropine, hydrochloric acid, iron, prostigmine, chloretone and pyridoxine.

Laboratory:

Urine: The color was not always red on this admission, occasionally being reported as amber or yellow. The porphobilinogen test was consistently positive, however. Specific gravity ranged from 1.006 to 1.023, and the reaction was usually acid. Albumin was present in small amounts in six of 13 specimens examined. White blood cells were never more than 15, and red blood cells never more than 4 per high power field centrifuged. Casts were not seen. *E. coli* was cultured once, and staphylococci twice. Quantitative urinary porphyrins were determined on four 24 hour urine specimens during this admission, through the courtesy of Dr. Cecil Watson, of the University of Minnesota School of Medicine, and were reported by Violet E. Hawkinson, of the Chemistry Department, to whom our thanks are due. The results were:

	Urinary Uroporphyrin, gamma/24 hr. (Normal = 0)	Urinary Coproporphyrin, gamma/24 hr. (Normal = 100 gamma/24 hr.)
10–8–46	3,190	648
10–15–46	14,900	845
10–20–46	336	226
10–27–46	280	648

Blood: Hemoglobin varied between 11.0 and 13.0 gm., and red blood cells between 3.8 and 4.7 million. Sedimentation rate was as low as 8 mm./hr., and as high as 21. White blood cells ranged between 4,850 and 13,250, with no more than 67 per cent polymorphonuclears at any time. Eosinophils were noted for the first

time on this admission, being reported once as high as 8 per cent, and as 3 per cent on three separate occasions.

Blood Chemistry: Non-protein nitrogen fluctuated between 37 and 43, CO_2 between 47 and 69 vol. per cent, chlorides from 500 to 624, and total protein from 4.3 to 6.7, A/G ratio always being normal. Cholesterol was 214 and 250 on two occasions. Fasting sugar was 88 mg. Bilirubin was less than 0.8 mg. Bromsulfalein retention was 3 per cent in 45 minutes.

An oral glucose tolerance test was reported as follows: fasting, 135; one-half hour, 160; one hour, 150; two hours, 147; three hours, 144; four hours, 95; five hours, 113. Heterophil agglutinations were negative.

Cerebrospinal Fluid: Pressure, 120 mm. of H_2O; protein, 90 mg.; 17 mononuclears; sugar, 86; chloride, 616; Kahn, negative; mastic, negative.

Fourth Admission: Four weeks later, on March 22, 1947, the patient was readmitted because of leg and back pain. At this time there were marked asthenia, distal extremity weakness and absence of reflexes. The skin was somewhat brown generally, and the urine was still tinted red. At this time, the patient was able to extend her fingers and to dorsiflex her right foot but not her left. The symptoms continued much as before, complicated by the previously suspected Demerol addiction. Two weeks after hospital admission, her respirations became very feeble and dropped frequently to eight a minute, with intervening periods of apnea. On the seventeenth hospital day, the patient was using her accessory respiratory muscles, there was stridor, and the swallowing and gag reflexes were absent. The Demerol was discontinued and she became hallucinatory, with marked emotional imbalance. The sweating around the lips continued to be present at intervals, and abdominal distention was noted, although peristalsis was present and there was no abdominal tenderness. On April 20, three weeks after admission, cyanosis was observed and the respiratory rate became extremely rapid. Laryngoscopy revealed relaxed vocal chords, which nevertheless approximated in the midline, and it was thought that there was both abductor and tensor weakness. On April 27, four weeks after admission, tracheal obstruction was thought to be present. The patient was moribund, with cyanosis and stridor, and accordingly tracheotomy was performed. Not immediately, but over the next few days, improvement was pronounced, and 12 days later she was no longer hallucinating, her appetite was good and she was ingesting 2,000 calories daily. On the forty-second hospital day, 12 days after the tracheotomy, she still required 400 mg. of Demerol for pain, as she had on many days previously, but on the day following required none, and none was demanded on any day subsequently. No withdrawal symptoms appeared. The tracheotomy tube was plugged and five days thereafter removed. During the entire next month, she seemed to gain somewhat in muscle power and was given physiotherapy, but she still complained of muscle pain and of hot flashes. On some occasions, it was noted that her urine was so deeply pigmented that it was almost black.

On July 9, four and a half months after admission, swelling of the lower abdomen was noted and colostrum was found to be present. Although pregnancy was previously unsuspected, it was obvious that she was in the twentieth to twenty-second week. Conception must have occurred between March 2 and March 22, prior to her fourth hospital admission. On July 27, four months after admission, she was discharged able to eat, and to walk with the aid of crutches.

The pulse during this admission ranged from 110 to 180 at its highest level daily. Temperature was occasionally as high as 101.6° F. Blood pressure fluctuated from 110/60 to 140/100. The pulse rate did not drop significantly at the time of clinical improvement following tracheotomy, but the blood pressure did drop to 90/60.

Medications consisted of Demerol, up to 400 mg. daily, other opiates and paral-

dehyde (these before the improvement following tracheotomy, none after), penicillin, liver and alkalizing agents.

Laboratory:

Urine: The color was more frequently yellow, although still red on occasion and once almost black. Porphobilinogen was always present. A trace of albumin was noted twice; up to 20 white blood cells and occasional red blood cells were seen. Bacteria were frequently observed. Phenolsulfonphthalein excretion was 60 per cent in two hours.

Blood: Hemoglobin ranged from 11.5 to 13.5 gm., and red blood cells from 3.6 to 4.8 million. White blood cells were recorded from 5,500 to 9,900, with from 54 per cent to 64 per cent polymorphonuclears, and 2 per cent or less of eosinophils. Sedimentation rate was 28 and 24 on two occasions. MCV was calculated on one occasion as 99, and MCH concentration as 33.

Blood Chemistry: Non-protein nitrogen ranged from 28 to 35; CO_2 was 49; total serum protein was from 4.9 to 6.8, with normal A/G ratio. Bromsulfalein retention was 12 per cent in 45 minutes.

Metabolism test was plus 31 per cent, determined only once.

Two weeks after discharge she was seen in the Out-patient Department. She was eating well, walking, and her pregnancy was found to be progressing satisfactorily.

Fifth Admission: Three days after having been seen in the Out-patient Department on August 22, 1947, she was admitted with what were thought to be labor pains. At that time, the fetal heart rate was 148, while the patient's pulse ranged from 104 to 120. The pains stopped on the second day, and she was discharged two days later on August 24.

Sixth Admission: She was admitted again on November 23, 1947, in anticipation of her delivery, having gained 32 pounds in weight from a low of 66 in the early part of the year. At this time she had only rare lower abdominal pain.

She had regained considerable strength and was able to feed herself. She remained in the hospital for the next three weeks in good health. It was noted that the gain in weight involved principally her face and trunk, marked atrophy being present in all four extremities. Motor strength, however, had improved, and sensation to all modalities was normal. There were still no deep reflexes obtainable, although the plantar reflex was normal.

During all her hospital admissions, one of the striking observations was the persistent sinus tachycardia, confirmed by repeated cardiograms, unresponsive to any medication. On November 26, three days after her sixth admission, she was given 500 c.c. of whole blood and, as noted on chart 1, her pulse immediately approached normal and remained so for two days, only to become rapid again until she went into labor approximately 14 days later. Labor began spontaneously at 8:00 a.m. of the nineteenth hospital day. Membranes were ruptured at 8:50 that evening, and she was delivered 20 minutes later of a seven pound four ounce normal male child, in normal position. Ether was used as anesthetic, but no oxytocics were administered. The child had no icterus or cyanosis, and was normally formed. The mother seemed an entirely different person immediately after delivery; she was cheerful and coöperative, regained her strength, ate well and, except for her deformities, seemed to be in good health. The heart rate became normal and remained so. She was discharged 10 days later.

The pulse was elevated from 108 to 120 on the first few days of admission, dropped to 96 or below for two days following the transfusion, rose again to remain above 100 and often above 110 every day until delivery, when it dropped to about 100 or below and remained at that level. Her weight before delivery was 114.

Laboratory:

Urine: The color was amber on all examinations but one, but was consistently positive for porphobilinogen both before and after delivery. Albumin was not present. White blood cells were present in small numbers, and no red blood cells were seen.

Quantitative porphyrin excretion, reported again through the courtesy of Dr. Cecil Watson by the University of Minnesota Medical School, was as follows:

	Uroporphyrin, gamma/24 hr. (Normal = 0)	Coproporphyrin, gamma/24 hr. (Normal = 100 gamma/24 hr.)
12-11-47		
One day antepartum	300	398
12-20-47		
Eight days postpartum	205	231
1-12-48		
31 days postpartum	320	607

Blood: The hemoglobin was 9.5 gm. and red blood cells were 3.0 million on admission, but rose after transfusion to 13 gm. with 4.0 million red blood cells. White blood cells were from 7,300 to 13,200, with normal differentials and no eosinophils. Bromsulfalein was still retained to the extent of 18 per cent after 45 minutes.

On January 13, 1948, three weeks after discharge, a postpartum check revealed that pulse was 80, blood pressure was normal, and the patient was clinically well.

Seventh Admission: She was re-admitted on September 11, 1948, for lengthening of her heel tendons. She had had no symptoms whatsoever and had noted that her urine was dark only on rare occasions. She had gained weight, and her hand and wrist function were normal, although the right thumb was ankylosed at the base. She had been wearing braces and had been able to walk with their assistance and with crutches. Spastic flexion of the fingers, with normal function, intra-osseous atrophy, and fixation of the feet in plantar flexion were the only abnormalities noted. Muscle power was good, and there seemed to be no atrophy of the larger muscles. All deep reflexes continued to be absent, but sensation and position sense were good. On September 13, 1949, her Achilles tendons were lengthened under spinal anesthesia. The procedure, which lasted 88 minutes, was tolerated well. There were some nervousness and nausea and some degree of back pain following surgery, but the next day she was much improved and was discharged five days later.

Quantitative urinary coproporphyrin was 600 gamma/24 hr., and uroporphyrin 60 gamma/24 hr. on this admission. Porphobilinogen was still present, although the urine was not discolored. During the following months she was seen in the clinic and, except for delayed healing of the incision in the left Achilles region, she was well.

Discussion

The present case, although unusually prolonged, is typical of that described as acute porphyria, with abdominal pain and encephalitis as well as peripheral nerve disturbances, ultimately leading to respiratory as well as extensor motor paralysis. Recognition of the condition was rendered easy by the presence of non-bloody red discoloration of the urine, later demonstrated in the laboratory to contain porphobilinogen. The family was tested as far as was possible, and no porphobilinogen was noted in the urine of the patient's mother, a half sister or three children, the eldest of whom was eight years of age.

The elements of this case of particular interest, aside from its being apparently the third instance of porphyria, and the second of acute porphyria in which pregnancy has occurred, are those connected with the abatement of symptoms. The patient had been acutely ill from July, 1946, until April, 1947, with only short periods of moderate remission. On April 27, 1947, she was moribund with respiratory paralysis, and a tracheotomy was performed. In the next 12 days, clinical improvement was dramatic, and overnight she changed from a delirious, malnourished, pain-ridden patient requiring daily doses of up to 400 mg. of Demerol, to a cheerful, apparently convalescent individual. This change corresponded to about the sixth to eighth week of pregnancy, the patient having been home from March 2 to March 22. Although clinical improvement began at this time, the drop in the persistently rapid pulse rate (chart 1) did not occur until a transfusion was given seven months later. The slowing of the pulse was only temporary following the transfusion, but it became permanent immediately following delivery.

These observations provoke speculation concerning the relation of the symptoms of porphyria to the degree of oxygenation of the tissues. The first improvement in this patient seemed to be associated either with the tracheotomy procedure or with the development of the circulation and blood-forming organs of the fetus within her. The second transitory improvement followed a blood transfusion. Permanent improvement in clinical symptoms (from December, 1947, until the present—February, 1950) followed immediately upon delivery of her child. The relationship of the last phenomenon is difficult to explain, but the others may quite possibly have pertinence in view of the rôle which the porphyrin nucleus plays in the hemoglobin molecule. In association with the clinical improvement, there was less frequent discoloration of the urine, but uroporphyrin and coproporphyrin and porphobilinogen continued to be excreted in excess.

Conclusion

An exceptionally severe and protracted case of acute porphyria in a young woman, in whom pregnancy occurred during the acute phase of the illness, has been studied. Of interest are the facts that she completed her pregnancy uneventfully and that clinical improvement seemed to follow (1) emergency tracheotomy, (2) the development of the fetus to the age of six to eight weeks, (3) the administration of a transfusion, and (4) the delivery of the child.

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ARTERIOSCLEROSIS: ITS ROLE IN THE PATHOGENESIS OF RECTAL HEMORRHAGE: CASE REPORT WITH AUTOPSY FINDINGS *

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Arteriosclerosis has long been recognized as an infrequent cause of rectal hemorrhage. Although examples of such bleeding have been cited in the past, no case with conclusive proof has been reported in the literature. Consequently, the first case of fatal rectal hemorrhage arising from an arteriosclerotic middle hemorrhoidal artery and substantiated at autopsy is herein reported.

In listing the etiology of rectal bleeding, Finney [1] in 1912, Gant [4] in 1916, Zobel [3] in 1918, and, later, Westphal,[2] Griffiths,[5] Keith [6] and Frankfeldt [7] noted that arteriosclerosis might be the causative agent. To this, Frisch [8] added that bleeding in older people with arteriosclerosis might be sudden and massive but never protracted, and Baldwin [9] added that the bleeding was painless and symptomless. Singer [10] in 1912, Landsman [11] in 1918 and, some years later, Wright and Sherwood,[12] Detlefsen,[13] Bellon,[14] Gutmann [15] and Turell [16] included hypertension along with arteriosclerosis as possible causes of rectal bleeding. Some authors, as Lockhart-Mummery [17] in 1928, followed by Rendleman,[18] Ross,[19] Harris,[20] Smith,[21] and Spears and Pfeiffer [22] have associated hypertension with melena.

Case histories in which arteriosclerosis alone was the generative factor in rectal hemorrhage are few in number. Detlefsen [13] reported four cases in 1933 and Stone [23] one case in 1944. Linthicum [24] in 1928 remarked that he had seen six cases with bleeding from the rectum accompanied by both arteriosclerosis and hypertension. Lockhart-Mummery [25] reported one such case in 1938 "and Stone [23] another in 1944." Rectal hemorrhage produced by hypertension alone was described by Deglos [26] in one case in 1931, by Detlefsen [13] in one case in 1933, by Stone [23] in two cases in 1944 and noticed by Gutmann [15] in six cases in 1934.

Carnot [27] in 1931 reported in detail three cases of melena in hemiplegics, one of which terminated in death by exsanguination, and five additional cases of rectal bleeding in arteriosclerotics, and he stated that melena with arteriosclerosis was much less rare than one would be led to believe from the paucity of reports in the literature. He also observed that occasionally, when no cause could be found clinically, roentgenologically or operatively for the expulsion of large quantities of dark red blood from the anal canal, the rupture of a vessel due to arterial hypertension, especially in hemiplegics, should then be considered. This rupture would occur in a fragile vessel which was diseased or arteriosclerotic, and hypertension might or might not be an influencing factor. It was remarked by Scott [28] in 1937 that in fatal hemorrhage from the gastrointestinal tract, where there was no clinical evidence of malignant disease or extragastric conditions, the pathologic findings were insufficiently investigated.

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The above summary of the literature was compiled from references to rectal hemorrhage, melena, arteriosclerosis, hypertension and related subjects. The term "rectal bleeding" (or hemorrhage) as used in the literature does not always refer to bleeding originating in the rectum itself, but rather to bleeding from almost the entire length of the gastrointestinal tract—from varices in the esophagus at one end to external hemorrhoids at the other. Rectal bleeding may be produced by as diverse a list of causes as is possible to mention in a differential diagnosis. A partial enumeration includes ulcers; benign neoplasms, as polyps, adenomas; malignant neoplasms, as carcinomas, sarcomas, lymphomas; infectious diseases, as tuberculosis, typhoid, bacillary dysentery; parasitic diseases, as hookworm, amoebic dysentery; segmental ileo-colitis; trauma, as foreign objects, external violence; diverticulitis; blood dyscrasias, as purpuras, leukemias; drugs, as acetylsalicylic acid; systemic poisons; vascular disorders, as varices, thrombosis, arteriosclerosis, hypertension; and rectal diseases, as ulcerative proctitis, hemorrhoids, fissures, fistulas.

In hemorrhage from the gastrointestinal tract, arteriosclerosis is rarely considered as the primary cause. Yet in 500 autopsies on arteriosclerotics, reported by Wartman [29] in 1933, 42 per cent showed arteriosclerosis of the vessels of the gastrointestinal tract. Furthermore, Wartman's figures revealed that *marked* arteriosclerosis of these vessels was one-fourth as frequent as *marked* arteriosclerosis of the cerebral vessels, and three-fifths as frequent as *marked* arteriosclerosis of the coronaries. Changes in the arteries in the walls of the rectum and the sigmoid can be seen clinically. Thus, with the aid of the sigmoidoscope, Linthicum [24] in 1928 saw thick, large blood vessels coursing under smooth, glistening mucosa, and, with the aid of the proctoscope, Schapiro and Astrachan [30] in 1947 described sclerotic vessels as appearing tortuous, corkscrew-like and beady.

Lockhart-Mummery [31] in 1934 aptly summarized hemorrhage from the terminal portion of the gastrointestinal tract when he wrote that massive hemorrhage might occur from the rectum or the colon in elderly individuals with advanced arteriosclerosis of the arteries and an elevated blood pressure, as a result of the rupture of a small blood vessel which could not be seen on sigmoidoscopic examination. Consequently, he added that diagnosis was difficult and could only be assumed from the state of the patient's vascular system.

Case Report

Present Illness: A 60 year old white male psychiatric patient, admitted to this hospital for domiciliary care, had a bowel movement and passed a small amount of bright red blood by rectum on July 20, 1948. There was no vomiting and no complaint of pain. Patient stated that he had hemorrhoids which were not painful and that bleeding had occurred occasionally. He weighed 130 pounds. His temperature was 99.6° F.; pulse, 104; respirations, 20. He looked dehydrated. Several blood pressure readings taken during the day recorded 125 mm. Hg systolic and 85 mm. diastolic, with a deviation of not more than 5 mm. of Hg in either the systolic or the diastolic readings. The abdomen was soft and nontender. Rectal examination showed bright red blood and clots around the anus and some red blood in the rectal ampulla. There was no pain on digital examination. Erythrocyte count was 3,350,000 per cu. mm. Hemoglobin was 9.5 gm. per 100 ml. (15.6 gm. = 100 per cent). Leukocyte count was 9,000 per cu. mm., with a normal differential.

Past History: Patient had had measles in childhood. He had served 20 months in World War I, during which time he had had a hemorrhoidectomy; he was discharged without any disability. His wife stated that in 1935 he had had stomach ulcers with hemorrhage. In 1937 he was hospitalized for two months because of a cerebrovascular accident. In August, 1945, he was admitted to a neuropsychiatric hospital for domiciliary care because of mental deterioration and left residual hemiplegia due to arteriosclerosis. At that time his weight was 165 pounds; blood pressure, 160/100 mm. Hg; pulse, 90; blood Kahn test, negative. A transurethral resection was done. In November, 1947, he was transferred to this hospital. The salient physical findings at that time were: weight, 144 pounds; numerous old scars over trunk and extremities; sclerosis of the retinal vessels; lungs, clear; no enlargement of the heart; systolic murmur in the mitral area; blood pressure, 132/100 mm. of Hg. Abdominal examination revealed a right rectus scar and a freely movable, pulsating mass to the left of the umbilicus. There was no history of vomiting, diarrhea, pain or other symptoms referable to the gastrointestinal tract. Neurologic examination was negative except for a residual left hemiplegia. Mentally, patient was deteriorated. There was no history of venereal disease, use of alcohol or drugs.

Laboratory Findings: Blood serologic test for syphilis was negative. There was a mild anemia. Leukocyte counts were within normal limits. Other blood studies and urinalyses were noncontributory.

Roentgenographic Findings: Left ventricular enlargement with some dilatation of the aorta and an aneurysm of the abdominal aorta with calcification. Healed old and recent fractures of the right and left wrists, right humerus, ribs and transverse processes of the vertebrae.

Hospital Course: Patient was placed on a Sippy diet for four weeks and then changed to a Meulengracht diet. His appetite was consistently good. He was given penicillin for two weeks. He was kept in bed and only occasionally allowed in a wheelchair. Temperature and respirations showed little change during this illness, but pulse and blood pressure varied with loss of blood. Sigmoidoscopic examination on August 10 disclosed polyps in the anal canal and blood clots in the rectal ampulla. No ulcerations or bleeding points were seen. The patient had numerous episodes of recurrent hemorrhages from the rectum and tarry stools which lasted for six weeks, as indicated in the accompanying table. At no time was there hematemesis or abdominal distress. Shortly after midnight on September 10, patient had a massive rectal hemorrhage of bright red blood and large blood clots and went into shock for which he was given intravenous fluids and blood plasma. He rallied, talked for a while, then relapsed into shock and died an hour and a half after the hemorrhage.

Clinical Impressions: Hemorrhage, gastrointestinal tract, site undetermined; possible malignancy or ulceration of large intestine; possible bleeding hemorrhoids.

Autopsy: Necropsy was performed seven hours after death. The following report includes only the relevant findings of the case.

Gross Description: The *body* was that of an emaciated white man, 60 years of age, 71 inches in length and approximately 130 pounds in weight. The skin was dry and loose. Irregular hemorrhoidal tags protruded and a small amount of bright red blood exuded from the anal orifice. The *peritoneal cavity* contained a thin-walled mesenteric cyst filled with 10 ml. of straw-colored fluid attached to the inferior border of the duodenum and a few thin fibrous bands which bound the liver to the rectus scar. Within the *pleural cavity* were fibrous adhesions which were more widespread on the right. The *lungs* contained an old scar in the right apex measuring 1.2 cm., and thick, tenacious mucus in the small bronchioles. The *heart* weighed 370 gm. The left ventricle and atrium were slightly dilated. The mitral ring measured 13.0 cm., the aortic ring, 8.2 cm. and their leaflets were opaque and thickened, especially at their bases. The aortic leaflets were fused at the commissures. The

chordae tendineae were short and thick. The myocardium was pale red, flabby and interspersed with diffuse, gray-white bands of tissue. The coronary arteries were widened at the ostia but narrowed in their lumina by atheromatous plaques. *Arteries:* There was severe arteriosclerosis of the aorta and of all its branches except the renal vessels. The pulmonary arteries were involved to a lesser extent. The abdominal aorta, near its bifurcation, contained a rounded aneurysmal sac measuring 6.0 cm. in diameter which was filled with a grayish red laminated thrombus. The *stomach, duodenum, small and large intestines* were thin-walled, and their rugae and folds were flattened. No ulcers, scars or bleeding points were seen. The ileum contained occasional petechiae. The mucosa of the rectosigmoid appeared dark red to reddish blue. *Rectum:* The rectal mucosa, 5.5 cm. from the anorectal junction, was interrupted around its circumference, and its proximal edge was slightly retracted, exposing the

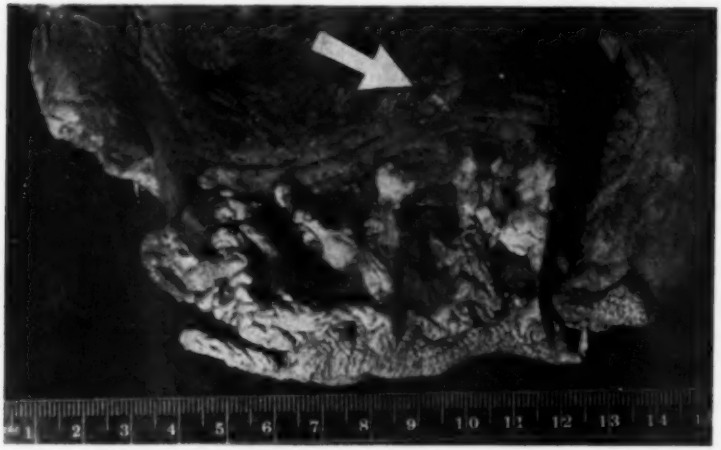

FIG. 1. Rectum. The loosened edge of the mucosa is reflected to expose the branch of the middle hemorrhoidal artery and its open lumen (arrow) from which hemorrhages occurred.

muscle layers. Hidden from view by the retracted edge of the mucosa was an artery, 2 mm. in outside diameter, whose open lumen protruded above the denuded muscle layers (figure 1). The lumen of the vessel was free from blood and clots. The vessel wall was rigid and irregularly thickened, and its intima was fragile. At the anorectal junction there were polypoid masses of gray-white tissue and dilated hemorrhoidal veins with no evidence of ulceration or bleeding. The right *kidney* weighed 150 gm. and the left 210 gm., and their surfaces were finely granular. The *brain* was edematous. The vertebral and cerebral arteries were conspicuously dilated, those at the base measuring approximately 1 cm. in outside diameter. Their walls were rigid, sclerotic and thickened.

Microscopic Description. Heart: The myocardium and endocardium were diffusely fibrotic and hyalinized and contained small foci of lymphocytes. The epicardium was thickened by an increase of fibrous tissue. The coronary arteries were somewhat calcified and extensively thickened by an increase of collagenous connective tissue, particularly in the intima. There was widespread hyalinization of the wall

of the aorta. *Lungs* were emphysematous. The walls of the pulmonary arteries were greatly thickened by an increase of collagenous connective tissue. *Spleen:* The arterioles showed marked thickening and hyalinization. *Kidneys:* Cortex contained focal areas of fibrosis, with diffuse collections of lymphocytes at the periphery, intact glomeruli and many dilated, convoluted tubules. Frequent hyaline casts were present within the tubules of the cortex and the medulla. There was severe sclerosis of the arterioles. Sections through various areas of the *stomach, pylorus* and *duodenum* disclosed thin walls and fewer and smaller mucous glands than are normally seen. The walls contained diffuse collections and the serosa, perivascular collections of lymphocytes, plasma cells, histiocytes and frequent polymorphonuclear leukocytes. In the mucosa and the submucosa there were increased deposits of collagenous connective tissue and thickened arterioles which showed fibrinoid degeneration of the intima. Elastica and van Gieson staining did not demonstrate elastic fibers in many of these arterioles. One submucosal vessel had a recent thrombus with partial organization at the periphery. *Rectum:* Sections through the region where the mucosa was interrupted in the gross specimen disclosed that the submucosa was separated from the muscle layer and that the apposing surfaces thus created were necrotic and contained diffuse collections of plasma cells, lymphocytes and frequent polymorphonuclear leukocytes. The *artery* which protruded above the muscle layer in the gross specimen microscopically revealed irregular thickening of the wall and a patent lumen containing a small amount of serum. Some sections showed necrosis of the entire thickness of the vessel wall, while others showed necrosis only of the intima. The necrotic areas were granular, stained pink to pinkish blue, contained nuclear fragments and exhibited only a few elastic fibers with the elastica and van Gieson stains. Within the wall of this artery, particularly in its outer portion, was an exudate, continuous with the exudate in the submucosa and muscle coats, composed of plasma cells, lymphocytes and frequent polymorphonuclear leukocytes.

Brain: The brain and spinal cord showed diffuse atrophy and moderate gliosis. The arteries and arterioles were thickened and their intima showed fibrinoid degeneration.

Anatomical Diagnoses: Generalized arteriosclerosis of: the aorta with aneurysm and thrombosis of the abdominal aorta; the coronary arteries with occlusion; the cerebral arteries; the iliacs; the middle hemorrhoidal artery with necrosis and hemorrhage. Arteriosclerosis of the kidneys. Hypertrophy and dilatation of the left ventricle. Fibrosis and thickening of the myocardium, the mitral and aortic valves. Necrosis of the rectal mucosa with acute inflammation. Hemorrhoids. Anal polyps. Emaciation.

Discussion

Fatal hemorrhage from an arteriosclerotic hemorrhoidal artery has not been reported prior to this case. In this instance there was arteriosclerosis of the entire arterial wall, necrosis (with resultant weakening) of the segment of the vessel extending beyond the muscle coats and, finally, hemorrhage. The ill-nourished rectal mucosa, subjected to the trauma of the continual passage of feces, undoubtedly gave way at the site of the old hemorrhoidectomy scar, creating the circular separation of the mucosa. Bacteria of the intestinal tract invaded the deep tissues at the zone of mucosal separation and caused inflammation and necrosis of the exposed surfaces of the submucosa, the muscularis and the involved artery. Thus, degeneration of the hemorrhoidal artery was produced by a sequence of events, beginning with arteriosclerosis which brought about poor tissue nutrition and decreased tissue resistance to fecal trauma, followed, in turn, by infection and inflammation, and ending in necrosis.

The patient obviously had severe arteriosclerosis during life, as manifested by his hemiplegia and psychosis, the outcome of a cerebrovascular accident; his mild hypertension, and his poor nutritional state, evidenced by his dry, thin, loose skin and moderate loss of weight. Calcification of the entire aorta and an aneurysm of the abdominal aorta were apparent on roentgenologic examination. The autopsy gave conclusive proof, both grossly and microscopically, of the generalized extreme arteriosclerosis and arteriolosclerosis.

The patient presented a baffling clinical picture. First, the present illness of repeated rectal hemorrhage was antedated by 13 years by a history of peptic ulcer and hemorrhage and by 31 years by a hemorrhoidectomy. Second, the usual criteria for determining the site of the gastrointestinal hemorrhage from the color

TABLE I

Episodes of Rectal Hemorrhage

Date	Number of Tarry Stools	Hemorrhage from Rectum	Intravenous Fluids
7-20		1 small, bright red 1 copious, dark red with clots	
7-21		2 small, dark red with clots 1 copious, dark red	500 ml. whole blood
7-22	1	1 copious, bright red 1 moderate, dark red	1,000 ml. 10% glucose 1,000 ml. 5% glucose 500 ml. whole blood
7-23	5	1 small, bright red	
7-24	2	2 small, bright red	1,000 ml. 5% glucose
7-25	4	1 small, dark red	
7-26	3		
8-7		Moderate, bright red	500 ml. whole blood
8-8	1 (with bloody mucus)	1 small, dark red	250 ml. plasma
8-9	4	1 small, dark red	
8-10	4	Several episodes, copious, bright red with clots	500 ml. whole blood
8-11	1	Several episodes, small, dark red	500 ml. whole blood
8-13	3 (2 were bright red)	1 moderate, dark red	
8-14	2 (bright red)		
8-15			500 ml. whole blood
8-17	5 (1 was bright red)		
8-18	1		500 ml. whole blood
8-19	3		
8-20	3		
8-21	1		
8-23	1		500 ml. whole blood
8-28	1	1 small, bright red	
8-29	3 (tinged with bright red)		300 ml. suspension washed red cells
8-30	1		
9-3		Moderate, bright red	
9-5	2 (1 bright red)		
9-6		1 copious, bright red	
9-8	1 (bright red)	1 copious, bright red	
9-9		1 small, bright red	
9-10		Massive, bright red with several large clots	500 ml. plasma 1,000 ml. 10% glucose

of the blood were not applicable in this case, since the blood varied from bright to dark red, and the stools from tarry to bright red (see table). Other than bleeding, there were no gastrointestinal symptoms and no evidence sigmoidoscopically of ulcers or scars to suggest ulcerative proctitis or colitis. This was borne out at autopsy when, on careful searching, no ulcers or scars were detected anywhere in the digestive system. However, in the rectum there was a break in the continuity of the mucosa, and the tissues adjacent to the break were edematous and congested. Since the submucosa was partially adherent to the muscle coats, the affected artery could not be seen. Spurting, usually observed from an open artery, was prevented in this case by the tampon effect of the adherent, edematous, congested mucosa and submucosa overlying the rigid artery. Instead, the blood accumulated in the deep tissues until its volume, and hence its pressure, at times augmented by the passage of feces, became sufficiently great to detach the submucosa from the muscle coats and expel the pool of blood. After such repeated bouts of hemorrhage, the overlying mucosa became undermined and loosened, and the tampon effect upon the artery was decreased. The rigidity of the arteriosclerotic vessel kept its lumen patent and permitted an almost continuous flow of blood (table 1). Thus, owing to a hidden, ruptured arteriosclerotic hemorrhoidal artery, the patient's insidious exsanguination was virtually impossible to diagnose and control.

Hemorrhage from a bleeding arteriosclerotic artery of the gastrointestinal tract is much more difficult to recognize and localize than hemorrhage in the brain, infarction of the heart or rupture of an aortic aneurysm due to arteriosclerosis, and is rarely considered in a differential diagnosis. Yet Wartman's [29] figures indicate that marked arteriosclerosis of the arteries of the digestive system is a rather frequent finding. In recent years a number of publications have appeared specifically implicating arteriosclerosis as the cause of gastrointestinal hemorrhage from the mesenteric arteries. This is consistent with the observations that the incidence of arteriosclerosis is increasing in a population whose life span is continuously lengthening. Therefore, in hemorrhage from the rectum, especially in elderly individuals, arteriosclerosis, with or without hypertension, should be considered in a differential diagnosis.

SUMMARY

1. The first case of fatal rectal hemorrhage from an arteriosclerotic hemorrhoidal artery confirmed at autopsy is reported.

2. A summary of a thorough search of the literature on the subject of rectal hemorrhage caused by arteriosclerosis is presented.

3. In hemorrhage from the rectum, especially in elderly individuals, arteriosclerosis, with or without hypertension, should be considered in a differential diagnosis.

4. More cases of hemorrhage from arteriosclerotic arteries of the rectum may be expected than have been reported previously because of the increase in incidence of arteriosclerosis in a population whose older age group is steadily growing in number.

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EDITORIAL

THE QUESTION OF CEREBRAL ANGIOSPASM

VASOSPASM has become a clinical cliché—a glib device to explain what at first seems to be otherwise inexplicable. Time and again we encounter, in books, in papers and in consultation, phrases that echo Osler's words, "the ephemeral nature of the attacks can scarcely be explained in any other way." Arterial spasm has become entrenched in our minds and texts as the underlying mechanism of transient cerebral syndromes. That this acceptance is hasty, uncritical and unnecessary, becomes evident from a consideration of known facts.

Cogent arguments against the acceptance of angiospasm as the mechanism of transient hypertensive crises have been advanced by Pickering.[1] He argues that the hypothesis of spasm is (1) improbable, judging by the nature of the vessels concerned; and (2) unnecessary, since an organic obstructive mechanism, namely, cerebral embolism, is known to produce precisely similar transient syndromes.

In the development of his argument he points out the following data: first, the cerebral arteries are not structurally adapted for marked constriction; anatomists have long wondered at the thinness of their walls, and it has been pointed out that their medial coats are largely composed of collagen with muscle scant or absent. Second, when it became possible to measure the contractility of pial vessels, it was found [2] that stimulation of the cervical sympathetic reduced the luminal diameter of pial vessels by a mere 7 per cent, while an artery of comparable size in the skin of the ear had its internal diameter reduced by 56 per cent. Adrenaline applied locally constricted cerebral arteries only feebly. Again, intravenous injection of adrenaline *increased* the luminal diameter of pial vessels by 4 per cent, whereas the cutaneous artery was constricted by 26 per cent. Thus from both anatomical and physiological studies the cerebral arteries appear to be feebly contractile and "clearly the hypothesis of local spasm of a cerebral artery, intense enough to produce paralysis of nervous function and ultimately necrosis of cerebral tissue, is not one to be adopted if a reasonable alternative can be put forward."

The next step in Pickering's logical thesis is to outline a series of cases of hypertensive encephalopathy, in whom the mechanism of transient attacks is popularly accepted to be spasm. Duration of symptoms in this series ranged from several minutes to several months. It is evident from

[1] Pickering, G. W.: Transient cerebral paralysis in hypertension and in cerebral embolism, J. A. M. A. 137: 423, 1948.

[2] Forbes, H. S., Finley, K. H., and Nason, G. I.: Cerebral circulation; action of epinephrine on pial vessels; action of pituitary and pitressin on pial vessels; vasomotor response in pia and in skin, Arch. Neurol. and Psychiat. 30: 957, 1933.

the examination of such a series that there is no clear-cut dividing line between cerebral paralyses that are transient and those that clear up more slowly leaving a residue. He then outlines for comparison a series of patients with auricular fibrillation, most of them under the age of fifty and with mitral stenosis. In this series a similar assortment of cerebral accidents occurred which may reasonably be presumed to be embolic. Again some paralyses were fleeting, while others were more enduring with residual lesions; and again no dividing line could be drawn between the transient and more lasting syndromes. The duration of symptoms in this series ranged from 30 minutes to several months. Proof of embolism by autopsy was afforded only in one case where death occurred within 24 hours of the cerebral accident. But, as Pickering points out, this is no argument against his conclusions as it is thoroughly proved and well accepted that the great majority of vascular occlusions occurring in the course of auricular fibrillation complicating mitral stenosis are due to embolism.

Pickering discusses the possible mechanisms which can account for the retreat of cerebral symptoms following the occlusion of an artery. Whatever the cause of the occlusion three restorative mechanisms can be postulated: (1) hemorrhage or edema initially surrounding ischemic brain tissue is gradually removed; (2) collateral vessels open and restore circulation to all or part of the ischemic territory; and (3) the obstructing clot is recanalized. In embolism a fourth process is admissible, that the embolus moves on or is forced into a side branch.

The absorption of hemorrhage and edema, and the recanalization of clot are immediately excluded on time relations alone in explanation of transitory attacks. Further, *all* emboli can scarcely be expected to dislodge themselves and move on. Therefore at least some instances of rapid recovery must be explained by the remaining process—the opening of collateral sources of blood supply. This is obviously just as acceptable in the explanation of the clearing of symptoms following thrombosis as following embolism.

Pickering summarizes in these words, "cerebral attacks occurring in patients with mitral stenosis and auricular fibrillation are similar in kind and duration to those occurring in severe hypertension. In both there may be a sudden paralysis of cerebral origin which clears completely in an hour or so or clears more slowly leaving a prolonged or permanent disability. There is no clear division in either series between paralysis that is completely and quickly reversible and paralysis with a permanent residuum." He points out that his is no new suggestion, for Jackson,[3] as long ago as 1880, wrote "transient paralysis may be owing to a small clot or to softening from blocking of a small vessel." Pickering believes that the actual mechanism of occlusion in hypertensive crises may be of several kinds: a thrombus may form on a preëxisting cushion of intimal thickening; hemorrhage may

[3] Jackson, J. H.: On a case of temporary left hemiplegia, Brain **3**: 433, 1880.

occur into the arterial wall; or acute fibrinoid necrosis may block the vascular lumen. All these forms of arterial closure are known to occur in hypertension and may logically be invoked as the manner of occlusion in the cerebral arteries.

This reasoning leaves unexplained, however, the pathogenesis of repeated transient symptoms related to the same topographical area of the brain, and presumably the same vessels of supply, such as repeated weakness of the same arm, or aphasia, with complete recovery in the intervals. One of Pickering's cases was of this type—eight attacks of left hemiparesis in six years occurred in a woman of 41 who had mitral stenosis and auricular fibrillation. As he says "it is inconceivable that eight separate emboli were delivered to precisely the same small vascular territory and to that only."

For such syndromes Denny-Brown [4] has recently offered a compelling explanation. He describes what he calls "the syndrome of chronic carotid occlusion." Gradual, chronic stenosis of the carotid artery produces "a state of episodic insufficiency in the circle of Willis, which is responsible for recurrent attacks of paralytic phenomena." He believes that this syndrome is more common than is generally believed, and claims to have studied eight cases of prolonged stenosis of the internal carotid artery in the last two years. He reports four of these, and one of them is remarkable for the number and transience of attacks. This 52 year old male patient suffered from seven attacks of left hemiplegia in as many months, most of them occurring on awakening from sleep, and each attack passing off in fifteen to thirty minutes. Angiography revealed great narrowing of the right internal carotid system. In the other three cases less transient symptoms and less frequent recurrences were recorded; in each the internal carotid of the side involved was completely occluded. Altogether more than forty cases of such non-traumatic carotid occlusion have been published, and among the more recent of these are the six cases reported in 1949 by Ameli and Ashby.[5] Interestingly the great majority of such thromboses occur in the *left* internal carotid.

Some of the reported cases have had symptoms provoked by effort and relieved by rest, thus providing a nice cerebral analogy to the effort-provoked ischemic syndromes of angina and intermittent claudication.

A number of cases of acute occlusion of the basilar artery, by embolism or thrombosis, were observed by Kubik and Adams.[6] Some of those in whom thrombosis was the occlusive mechanism had had repeated premonitory cerebral episodes, notably dizzy spells, for months or years before the final acute occlusion closed the eventful history. Denny-Brown records

[4] Denny-Brown, D.: The treatment of recurrent cerebrovascular symptoms and the question of "vasospasm," Med. Clin. N. Am. **35**: 1457, 1951.

[5] Ameli, N. O., and Ashby, D. W.: Non-traumatic thrombosis of the carotid artery, Lancet **2**: 1078, 1949.

[6] Kubik, C. S., and Adams, R. D.: Occlusion of the basilar artery—a clinical and pathological study, Brain **69**: 73, 1946.

two cases of more chronic stenosis of the basilar artery. One of these was characterized by repeated cerebral attacks including spells of unconsciousness, transient blindness, and aphasia. At autopsy the basilar artery at one point was narrowed by an atheroma to a mere two millimeter caliber, which was further diminished by a layer of organizing clot.

It is thus clear that proved organic occlusions can produce transient cerebral syndromes. It may here be reëmphasized that the two criteria so glibly proffered and so uncritically accepted as the hallmarks of spasm—brief duration and complete recovery—are no argument for spasm at all. Both these criteria are amply satisfied by well documented examples of both acute and chronic organic vascular occlusion.

Denny-Brown suggests that when the repeated transient disorder is in the nature of "weakness and numbness of an arm, with dysarthria or dysphasia," occlusion of one internal carotid should be suspected. When the transient episodes comprise "dizziness, total blindness, weakness of limbs, leading to loss of consciousness if severe," suspicion of basilar artery occlusion should be aroused.

He describes two useful clinical tests in the diagnosis of internal carotid occlusion: (1) light pressure on the eyeball of the affected side during ophthalmoscopic examination will cause the retinal vessels to pulsate, while increasing pressure will empty them; and (2) manual compression of the internal carotid on the side of the paralysis (i.e., of the unobstructed carotid) causes blanching of the vessels in the opposite fundus.

One of the important practical lessons to be learned from the observation of these syndromes is the grave danger of a lowered blood pressure. Among Denny-Brown's cases it was noticeable that falls in blood pressure seriously aggravated the already compromised circulation so that cerebral symptoms were directly related to sleep in five cases, gastrointestinal hemorrhage in two cases, and syncope in one. The use of vasodilators which are frequently administered for control of supposed vasospasm may therefore prove dangerous. In one case a disastrous renewal of cerebral symptoms (and a myocardial infarction in addition) followed the use of a peripheral vasodilator for associated intermittent claudication.

There remains another clinical picture unexplained by any of the pathogenetic mechanisms so far considered. This is characterized by rapidly repeated attacks occurring in the space of a few hours, unpreceded by premonitory symptoms and followed by a prolonged period of freedom from symptoms. A good example of this type was described by Foster Kennedy and his colleagues [7]: a man of 82 with normal blood pressure suddenly had 26 episodes of dysphasia and right hemiplegia in 36 hours. He then had no further attacks during the subsequent three years.

Such attacks are tempting bait indeed to the advocates of spasm, as it

[7] Kennedy, F., Wortis, S. B., and Wortis, H.: The clinical evidence for cerebral vasomotor changes, Proc. A. Research Nerv. and Ment. Dis. **18**: 670, 1937.

does not seem possible to explain them on the basis of organic occlusions. Repeated vascular occlusions involving the same territory are clearly inadequate in explanation, and chronic occlusion of the internal carotid or basilar artery could scarcely be expected to produce the sudden appearance of frequent attacks with prolonged subsequent freedom. On purely theoretical grounds it is not impossible, however, to explain this sequence of events without invoking spasm. For if it is true that a transient syndrome may be the result of organic closure followed by more or less rapid rescue by the collateral vessels, it is not inconceivable that repeated attacks might be produced by subsequent fluctuations in the adequacy of collateral blood supply. Such an explanation at least has the virtue of invoking only known mechanisms. For while there is no evidence that spasm can occur in any but the most abnormal circumstances, it is well known that the cerebral vessels maintain a normal modest tonus beyond which they can be widely dilated. The stimuli best known to effect such dilatation are anoxemia and excess of carbon dioxide.[8] Such an explanation then involves an alternation between dilatation and normal tone on the part of collateral vessels with consequent waxing and waning of blood supply to the infarcted area.

We have seen that spasm is an unlikely mechanism, and that most cerebral syndromes can be otherwise explained. There is, however, at least one clear-cut piece of evidence that cerebral arteries are *capable* of severe spasm despite their tenuous structure. In patients who had been subjected to epileptiform convulsions from electrical stimulation of the cortex, Penfield observed localized spasm in pial arteries so intense that pulsation was completely obliterated.[9] This clearly represented a reaction to a grossly abnormal situation, but nevertheless demonstrated the intrinsic capacity of these vessels, given the adequate stimulus, to develop obliterative spasm.

Undoubtedly much more work must be done before we can diagnose with confidence and accuracy the underlying mechanism of each and every brief cerebral syndrome. In the present state of our knowledge there are many unexplained facets to the problem. Thus, without accepting angiospasm, it is difficult to explain the dramatic successes claimed by Russek and Zohman[10] in patients with frequently repeated cerebral episodes. They used large doses of papaverine and relieved the symptoms of patients who had been suffering from several attacks daily.

From the point of view of therapy it is clear that the differentiation of the underlying mechanisms is assuming more and more important proportions. From Denny-Brown's observations vasodilators would appear to be positively dangerous in one form of transient cerebral attack; yet from

[8] Schmidt, C. F.: The cerebral circulation in health and disease, 1950, C. C Thomas, Springfield, Ill., p. 27.

[9] Penfield, W.: The circulation of the epileptic brain, Proc. A. Research Nerv. and Ment. Dis. 18: 605, 1937.

[10] Russek, H. I., and Zohman, B. L.: Papaverine in cerebral angiospasm (vascular encephalopathy), J. A. M. A. 136: 930, 1948.

the study of Russek and Zohman with clinically similar syndromes a vasodilator can be extremely efficacious treatment. Again with the increased availability of anticoagulant drugs in recent years the certain differentiation between cerebral hemorrhage and thrombosis has assumed greater importance. Thus the question of underlying mechanisms in cerebral syndromes has rapidly become less academic and more practical.

It has been pointed out above that many standard texts, while admitting that the case for cerebral vasospasm is unproved, clearly accept and condone it as the probable mechanism of these syndromes. For example Alpers,[11] while recognizing the lack of convincing experimental evidence that significant spasm is likely, states "from a clinical point of view there is, nevertheless, a large group of cases in which the clinical phenomena are explainable only on the basis of vascular spasm." He then goes on to say that Pickering's argument does not explain "how a thrombus can be dissolved in a matter of hours." From the résumé of Pickering's discussion given above, it is clear that this is a hasty criticism begotten of failure to digest the proffered argument. The burden of Pickering's argument bears repeating: if a solid obstruction like an embolus can cause symptoms which pass off in minutes or hours, there is no reason why other forms of equally substantial obstruction cannot cause a similarly transient syndrome. There is no question of either embolus or thrombus dissolving; in each case the explanation of rapid improvement is the opening up of collateral channels of supply to the ischemic area.

Again, as eminent a vascular authority as Leriche[12] has recently reaffirmed the belief that some cerebral vascular manifestations cannot be accounted for by anything but local arterial spasm. The instances he quotes, however, are such as we have clearly seen may be the result of either acute or chronic organic vascular closure.

Among the welter of case reports in which the diagnosis of spasm is accepted unquestioningly, it is reassuring to read the opinion of a master as interested in the subject as Alvarez. He does not subscribe to spasm as the pathogenetic mechanism for any of what he picturesquely calls "little strokes" or "strokelets." In his words, "the one good thing about this idea of spasm in blood vessels is that oftentimes it serves to soften the blow for some timid patient and also for his physicians, who cannot bring themselves to accept the idea of a thrombosis."[13]

It is regrettable that the concept of spasm has been allowed to gain so firm a hold in the minds of so many. While it cannot yet be said that spasm is never the cause of transient syndromes, it can at least be asserted that it is a far less frequent cause than is commonly assumed and stated. Short-lived vascular attacks can almost always be explained, to quote Pickering

[11] Alpers, B. J.: Clinical neurology, 2nd ed., 1950, F. A. Davis Co., Philadelphia, p. 477.
[12] Leriche, R.: Treatment of embolism and thrombosis of the cerebral vessels, Brit. M. J. 1: 231, 1952.
[13] Alvarez, W. C.: The neuroses, 1951, W. B. Saunders Co., Philadelphia, p. 201.

again, "in terms of known pathological or physiological processes, without assuming that arteries behave like whimsical children (as children were understood before contemporary psychology) and react violently to a perfectly ordinary stimulus or to none at all." [14]

It might therefore well be recommended that the blind acceptance of vasospasm be discouraged, for such acceptance may well retard our understanding of the true nature of transient cerebral syndromes. While often useful, *a posteriori* arguments can also impede the progress of discovery, as the early belief that the world was flat surely delayed the recognition of its globularity. There can be no scientific justification for accepting such propositions as facts, and it would presumably be more to our credit not to take frequent refuge in an unnecessary improbability such as cerebral angiospasm.

H. J. L. M.

[14] Pickering, G. W.: Vascular spasm, Lancet 2: 845, 1951.

REVIEWS

First Annual Report on Stress. By HANS SELYE, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada), Professor and Director of the Institut de Médecine et de Chirurgie experimentales. Université de Montréal. 644 pages; 17 × 25 cm. Acta, Inc., Montreal, Canada. 1951. Price, $10.00, plus 34¢ mailing charges if ordered from publisher.

Writing with admirable candor and complete objectivity, Selye, as usual, has produced a brilliant defense of his General-Adaptation-Syndrome (G-A-S). Readers are amply warned in the very first sentence that "this book is admittedly not an unbiased and impersonal index of facts" and, with this qualification well understood, it can be recommended without hesitation. The style is delightfully informal in spots and his occasional and seemingly spontaneous asides as to how he met certain problems which arose in the writing of the book will certainly be appreciated by those confronted with similar situations. In other and longer stretches the book plods along in the inevitable and characteristic manner of its kind, a fact which probably causes the author more distress than the reader. Even so, no one interested in the subject can help but find it tremendously stimulating or fail to be affected by the enthusiasm of the author. It should be read with caution and discrimination, however, for it contains a bewildering array of theories, hypotheses and "hunches" about hypophyseal and adrenal cortical action that are apt to mislead anyone but the specialist in the field.

Obviously a great deal of time and thought have gone into the organization of this and other books by the same author, and one stands in awe of his prolific literary accomplishment. The bibliography includes all of the literature in the stress field which has appeared during the past year or so (together with some of the earlier papers, included for the sake of completeness)—a total of over 3,000 references, of which not more than 10 or 12 per cent were published before 1950. It is no mean task to incorporate such a mass of material into a single book without giving it the flavor of an abstract journal.

This volume, written as an appendix to an earlier one published in 1950 and entitled *Stress*, is designed to integrate this recent material into the G-A-S as developed by the author. This concept forms the central core of the book and it is the author's contention that many of the systemic diseases are, as he calls them, derailments of the G-A-S or the adaptative defenses of the organism against environmental stresses of all kinds. Involved in these adaptations are the adrenal cortex and the hypophysis, and possibly the adrenal medulla as well. When the organism is subjected to stress, the hypophysis liberates ACTH (and according to Selye possibly somatotrophic hormone, or STH, as well) which then stimulates the adrenal cortex to produce what Selye calls the mineralo-corticoids (M-Cs) and the gluco-corticoids (G-Cs). Under certain conditions and in certain animals, the M-Cs in excess produce the rheumatic and hypertensive diseases. Such a derailment of the G-A-S can be relieved by the G-Cs. Obviously when no derailment of the G-A-S occurs there is no disease. Selye also suggests that the release of M-C might possibly be under the control of STH, for STH seems to promote those conditions associated with excessive M-C secretions. Whether this results from stimulating M-C production by the cortex or sensitizing the peripheral tissue to M-C is not yet decided. The involvement of STH in the stress response is a new development and awaits corroboration.

The book is organized into two main parts, the first of which considers the gen-

eral physiology and pathology of stress along with an excellent and concise summary of Selye's views. It is well worth reading by anyone who wants to be informed in this field and it is by far the shortest section of the book. The second part is concerned with the special physiology and pathology of stress and embraces a tremendous range of subjects, including, to mention but a few, carbohydrate metabolism, enzyme action, salt and water metabolism, wound healing, and inflammation. The physician will be particularly interested in what Selye calls the "Diseases of Adaptation" as seen in the cardiovascular system, the respiratory system, the kidneys, the gastrointestinal tract and the liver, to name again only some of the more important categories. The implications in the treatment of hypertension by subtotal or complete bilateral adrenalectomy are of considerable theoretical importance since they support the view that hypertension is a Disease of Adaptation, due to a disturbance in the secretion of M-Cs.

One of the more interesting sections of the book is devoted to a discussion of the principal objections to the author's views and he not only conscientiously lists them all, but classifies them as well. Needless to say, he also answers them. One of the more important is, of course, the growing conviction in the minds of many investigators that desoxycorticosterone, which is presumably the M-C involved in the G-A-S, is not secreted by the adrenal cortex at all under physiological conditions. The long list of objections cited is, of course, eloquent proof in itself that the concept has by no means gained general acceptance among endocrinologists. On the other hand, there is no question that Selye's speculations have in themselves contributed greatly to the rapid advances being made in the field of stress physiology. The homeostasis concept, which was first brought into being by Claude Bernard and later developed and expanded by Walter Cannon, is now coming of age—thanks to the effort and insight of work such as this. If occasionally some of our thinking about these matters should advance faster than the facts warrant, it is nothing new in the history of science. It may very well be that the recognition of the real significance of homeostasis will be our era's greatest contribution to physiology and medicine.

DIETRICH C. SMITH

Angiocardiography: Annals of Roentgenology, Volume XX. By CHARLES T. DOTTER, M.D., Assistant Professor of Radiology, Cornell University Medical College, and ISRAEL STEINBERG, M.D., Assistant Clinical Professor of Radiology and Medicine, Cornell University Medical College. 304 pages; 20.5 × 27 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., New York. 1951. Price, $16.00.

Angiocardiography, although a recently developed technic, has come of age, and this excellent text attests to that fact. The authors carefully and thoroughly describe the method and its application in the study of various types of congenital and acquired heart disease and of certain pulmonary conditions. An understanding of the information obtained by angiocardiography serves as a firm foundation for the use of fluoroscopy in the study of cardiac conditions. The authors' approach is basic and frank; the dangers and limitations of the method are presented as well as the indications for its use and advantages to be obtained. The text is clearly written, with proper attention to detail. The illustrations and diagrams are instructive and clearly reproduced. Both authors and publisher should be complimented upon their production.

This book should be read by internists, cardiologists and roentgenologists, and is heartily recommended.

S. S.

A Textbook of Clinical Neurology. 3rd Ed. By J. M. NIELSEN, B.S., M.D., F.A.C.P. 709 pages; 18 × 26.5 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., New York. 1951. Price, $10.00.

Many aspects of neurology have seen advancement since the last edition of this book. Among these may be mentioned knowledge in the fields of polyneuritis and neuronitis, thanks mainly to recent studies with BAL and porphyria; the incrimination of the temporal lobe in psychomotor epilepsy and the consequent surgical approach to its treatment; the use of stellate ganglion block and intravenous procaine in the treatment of cerebral thrombosis and embolism; the subjects of poliomyelitis and central nervous system syphilis. The sections on these subjects have therefore been rewritten in the light of newly acquired knowledge.

New chapters on multiple sclerosis, the psychoneuroses and angiography have been included, while the chapter on electroencephalography has been revised and a section on electromyography added. Most of these new sections are well handled.

This book has many virtues. It is clearly and readably written, it is amply and graphically illustrated, a considerable bibliography is appended at the conclusion of each chapter, and the text contains a useful sprinkling of instructive case histories. A number of the sections and chapters are outstandingly well presented, among which the sections devoted to the pupils, to the lamination of the spinothalamic tracts and to syringomyelia, and the chapters on multiple sclerosis and on angiography, may well be singled out for special mention.

The book is not, however, above criticism. Clarity and readability would often be enhanced by the more judicious use of subheadings, and many sections are not as detailed and comprehensive as they should be in a volume of these impressive proportions. There is a distressingly consistent failure in the body of the text to refer the reader to the appropriate illustrations. The bibliography has some disturbing omissions—for example, after referring in some detail to the recent innovations of stellate ganglion block and intravenous procaine for the relief of cerebral vasospasm following vascular occlusion, the author fails to include references to this interesting and controversial subject among the chapter's bibliography of some 130 papers. The index, too, is not all it should be; for example, "monoplegia" is not to be found, thrombosis of the posterior inferior cerebellar artery is not included under "thrombosis," and von Hippel-Lindau disease, though referred to as such in the text on at least two occasions, is only to be found under "Lindau's disease."

Superficially this revised and reset edition is an attractive volume. It has, however, many of the physical faults that we are seeing with increasing frequency in medical works; one too often observes the tendency for externals to improve and formats to become impressive, while the inner soul remains unbettered. This particular book is bigger and heavier than its contents merit, and it is printed on the glossiest of paper for which no serious reader will thank the publisher.

Although many of these criticisms are minor, their multiplicity makes this an irritating text to read.

H. J. L. M.

A Study of Epilepsy in Its Clinical, Social and Genetic Aspects. By CARL HENRY ALSTROM. 284 pages; 16.5 × 24 cm. (paper bound). Ejnar Munksgaard, Nonnegade 6, Copenhagen. 1950. Price, 20 Swedish crowns.

This is a concise and informative book on the history of epilepsy over a period of 15 years in the Neurological Clinic and the Human Genetics of the Psychiatric Clinic of the Caroline Institute, Stockholm. It is a book which would be of most interest to one interested in epilepsy, and especially the genetic aspects. This study

covers the country of Sweden probably much more thoroughly than has been done in any state in the United States to the present time: however, in spite of this, it is only about one-third as large a series as any of our larger clinics set up for the seizure patient.

The completeness with which this study was carried out is remarkable, as in many cases as many as five to six generations had been traced very accurately through parish registers, hospitals, physicians, civil authorities and courts of law, especially the penal registers.

A new classification for epilepsy is suggested based on etiology—unknown, probable and known. This brings up questions as to how to classify cases with a history of epilepsy in the past generation or generations, who after a mild injury develop seizures. Why should some patients with mild head trauma develop seizures and other patients with similar or more severe head trauma not develop them?

It is of interest to note that eugenic legislation against the epileptic patient has had little effect in reducing the incidence of epilepsy. The comparison of the mentally unaffected epileptic with the general population as to education, social and occupational standards and criminality is excellent. It will help to counteract the present popular opinion on this matter. As to the epileptic personality, there is still much debate over this issue; and a great deal more work must be done in making comparisons with other chronically ill groups who have been definitely ostracized by the general population. Work done by Lennox certainly indicates that there is no so-called epileptic personality, and this makes one question the so-called "preservation and adhesiveness of thoughts and emotions" discussed here.

The hypothesis of epilepsy as a symptom of a pathological irritation of the central nervous system and not a disease per se is certainly in agreement with the present theories in this country. The genetics of this certainly is still in much confusion today. The fact of electroencephalograms showing dominant genetic traits must in spite of the disagreement by Alstrom, be considered important, as the series of Gibbs, Gibbs and Lennox has now become very large, showing similarity in patterns between one or the other parent and the affected child. The papers by Lennox on epilepsy in twins cannot be overlooked and deserve study by those called on to give eugenic advice.

R. W. B.

Surgical Practice of the Lahey Clinic. By Members of the Staff of the Lahey Clinic, Boston, Massachusetts. 1014 pages; 17 × 25.5 cm. W. B. Saunders Company, Philadelphia. 1951. Price, $15.00.

This volume of the Surgical Practice of the Lahey Clinic is splendidly organized. It contains many new operative procedures and follows an edition published ten years ago. Contributors are entirely from the Lahey Clinic. With each surgical procedure, there is a discussion of related physiology, anatomy, pre- and postoperative care. All types of surgery are discussed, including major specialized fields.

The book is liberally illustrated with photographs, drawings and charts. The bibliography is excellent.

A chapter is devoted to the problem of anesthesia with a discussion of special agents and technics, as well as cardiac arrest. A section on miscellaneous subjects, such as Menière's Disease; Exposure of the Facial Nerve; Anticoagulant Therapy, adds to the intrinsic value of the book. In its entirety, it represents an excellent addition to the field of surgical literature. It is invaluable as a precise reference to well accepted operative procedures as standardized at the Lahey Clinic.

G. H. Y.

Should I Retire? By GEORGE H. PRESTON, M.D. 181 pages; 14 × 20 cm. Rinehart & Co., Inc., New York. 1952. Price, $2.50.

Dr. Preston has discussed in common sense terms the psychological, financial and physical problems involved in planning for retirement. Those who are familiar with the author's earlier books, *Psychiatry for the Curious* and *The Substance of Mental Health*, will welcome again his facile style, apt use of colloquial phrases and the case illustrations in which we recognize our neighbors and ourselves.

The book is frank to say that some people can never retire successfully. However, the possibilities of making this adjustment can be increased by orienting our thinking in advance. Dr. Preston outlines some of the criteria for successful retirement and suggests ways of achieving them. He believes that one's personality and adaptability contribute more to a happy life than the amount of one's pension.

In the chapter entitled "Am I Retirement Minded" is a "test" to determine one's readiness to meet the change. It is one which both doctor and patient could well start practicing before retirement is forced upon them.

It is in this effort to become retirement minded that this little book can be of most usefulness. Whether this book makes retirement more attractive or not depends on one's own personality but it is good medicine for the patient who is faced with the inevitable change.

H. W. N.

BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Annual Report of the Librarian of Congress for Fiscal Year Ending June 30, 1950. 277 pages; 26.5 × 18.5 cm. 1951. United States Government Printing Office, Washington, D. C. Price, $2.25.

Aspetti Fisiopatologici Delle Strutture Acellulari Del Tessuto Connettivo—Dermatomiosite. By DOTT. VITTORIO BIANCHI. 155 pages; 25 × 18 cm. (paperbound). 1951. Ditta Luigi Pozzi, Rome.

The Auricular Arrhythmias. By MYRON PRINZMETAL, M.D., ELIOT CORDAY, M.D., ISIDOR C. BRILL, M.D., ROBERT W. OBLATH, M.D., H. E. KRUGER, and Associate Authors JOSHUA FIELDS, M.D., WALTER FLIEG, M.D., ALFRED GOLDMAN, M.D., HAROLD KARPMAN, A.B., S. REXFORD KENNAMER, M.D., JOHN A. OSBORNE, M.D., ALVIN L. SELLERS, M.D., and L. ALLEN SMITH, M.D. 387 pages; 28.5 × 22 cm. 1952. Charles C Thomas, Publisher, Springfield, Illinois. Price, $16.50.

Callander's Surgical Anatomy. 3rd Ed. By BARRY J. ANSON, M.A., Ph.D. (Med. Sc.), Professor of Anatomy, Northwestern University Medical School; and WALTER G. MADDOCK, M.S., M.D., F.A.C.S., Elcock Professor of Surgery, Northwestern University Medical School. 1,074 pages; 26 × 18 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $14.00.

Care of the Medical Patient: A Textbook for Nurses. By MARGENE O. FADDIS, R.N., M.A., Professor of Medical Nursing, Frances Payne Bolton School of Nursing, Western Reserve University, Cleveland, Ohio; and JOSEPH M. HAYMAN, JR., B.A., M.D., Professor of Medicine, School of Medicine, Western Reserve University, Cleveland, Ohio. 654 pages; 23.5 × 15.5 cm. 1952. McGraw-Hill Book Company, Inc., New York. Price, $4.50.

The Clinical Use of Fluid and Electrolyte. By JOHN H. BLAND, M.D., Assistant Professor of Medicine, University of Vermont College of Medicine. 259 pages; 28 × 21.5 cm. (paper-bound). 1952. W. B. Saunders Company, Philadelphia. Price, $6.50.

Connective Tissues: Transactions of the Second Conference, May 24–25, 1951, New York, N. Y. Edited by CHARLES RAGAN, Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y. 190 pages; 23.5 × 15.5 cm. 1952. Sponsored by the Josiah Macy, Jr., Foundation, New York, N. Y. Price, $3.50.

Le Cosidette Angiomesenchimopatie Reattive Diffuse. By PROF. ALBERTO MARMONT. 349 pages; 25 × 18 cm. (paper-bound). 1951. Ditta Luigi Pozzi, Rome.

The Diagnosis and Treatment of Intrathoracic New Growths. By MAURICE DAVIDSON, M.A., D.M., B.Ch. Oxon., F.R.C.P. Lond., Consulting Physician to the Brompton Hospital for Consumption and Diseases of the Chest, etc.; with a chapter on Radiotherapy by DAVID W. SMITHERS, M.D. Cantab., M.R.C.P. Lond., D.M.R., Professor of Radiotherapy, University of London, etc.; and a chapter on Operative Treatment by OSWALD S. TUBBS, M.A., M.B., B.Chir. Cantab., F.R.C.S. Eng., Thoracic Surgeon to St. Bartholomew's Hospital, etc. 260 pages; 25 × 17.5 cm. 1952. Oxford University Press, New York. Price, $8.75.

Doctors in Blue: The Medical History of the Union Army in the Civil War. By GEORGE WORTHINGTON ADAMS. 253 pages; 21.5 × 14 cm. 1952. Henry Schuman, Inc., New York. Price, $4.00.

Der Einfluss des Nervensystems auf Bau und Tätigkeit der Geschlechtsorgane des Menschen. By PROF. DR. MED. ET PHIL. H. STIEVE. 191 pages; 24.5 × 17.5 cm. 1952. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 36.–

Endocrine Functions of the Pancreas. By BERNARD ZIMMERMANN, M.D., Department of Surgery, University of Minnesota, Minneapolis, Minnesota. 82 pages; 22.5 × 14.5 cm. (limp leather binding). 1952. Charles C Thomas, Publisher, Springfield, Illinois. Price, $2.50.

Fluid Balance, A Clinical Manual. By CARL A. MOYER, M.D., Professor of Surgery, Washington University School of Medicine, St. Louis. 191 pages; 18.5 × 12.5 cm. 1952. The Year Book Publishers, Inc., Chicago. Price, $3.75.

La Funzione Emoblastica del Sistema Istiocitario. By CARLO BIANCHI. 280 pages, plus 79 pages of illustrations; 27.5 × 18 cm. (paper-bound). 1951. Istituto Bioterapico Carlevaro Editore, Parma. Price, Lire 3000.

Hippocrates on Intercourse and Pregnancy: An English Translation of "On Semen and on the Development of the Child." By TAGE U. H. ELLINGER, Sc.D., M.A.; with an introduction by ALAN F. GUTTMACHER, M.D. 128 pages; 16 × 11 cm. 1952. Henry Schuman, Inc., New York. Price, $2.50.

Klinik und Therapie der Vergiftungen. By SVEN MOESCHLIN. 430 pages; 24.5 × 17.5 cm. 1952. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 45.–

Klinische Elektrokardiographie. By DR. MAX HOLZMANN. 652 pages; 24.5 × 17.5 cm. 1952. Georg Thieme Verlag, Stuttgart. Price, Ganzleinen DM 69.60.

Liver Injury: Transactions of the Tenth Conference, May 21–22, 1951, New York, N. Y. Edited by F. W. HOFFBAUER, M.D., Department of Medicine, University of Minnesota Medical School, Minneapolis 14, Minnesota. 320 pages; 23.5 × 15.5 cm. 1951. Sponsored by the Josiah Macy, Jr., Foundation, New York, N. Y. 1951. Price, $3.75.

Manic-Depressive Psychosis and Allied Conditions. By LEOPOLD BELLAK, M.D., Clinical Assistant Professor of Psychiatry, New York Medical College, Fifth Avenue and Flower Hospitals; with BLAISE PASQUARELLI, M.D., Research Associate, New York State Psychiatric Institute; ERNEST PARKES, M.A., Instructor in Psychology, New York University; SONYA SOREL BELLAK, and the collaboration of SYDELL BRAVERMAN, M.A.; Foreword by WINFRED OVERHOLSER, M.D. 306 pages; 23.5 × 15.5 cm. 1952. Grune & Stratton, Inc., New York. Price, $9.75.

ℝ for Medical Writing: A Useful Guide to Principles and Practice of Effective Scientific Writing and Illustration. By EDWIN P. JORDAN, M.D., and WILLARD C. SHEPARD. 112 pages; 24 × 16 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $2.50.

Principles and Practice of Aviation Medicine. 3rd Ed. By HARRY G. ARMSTRONG, M.D., F.A.C.P., The Surgeon General, United States Air Force. 476 pages; 23.5 × 15.5 cm. 1952. The Williams & Wilkins Company, Baltimore. Price, $7.50.

Probleme der Schutzimpfung und die Bekämpfung der Rindertuberkulose. By PROF. DR. G. RAMON. 52 pages; 24 × 17 cm. (paper-bound). 1952. Georg Thieme Verlag, Stuttgart. Price, Karton. DM 7.20.

Problems of Consciousness: Transactions of the Second Conference, March 19–20, 1951, New York, N. Y. Edited by HAROLD A. ABRAMSON, M.D., Department of Physiology, College of Physicians and Surgeons, Columbia University, New York, N. Y. 178 pages; 23.5 × 15.5 cm. 1951. Sponsored by the Josiah Macy, Jr., Foundation, New York, N. Y. Price, $3.25.

Rheumatic Diseases: Based on the Proceedings of the Seventh International Congress on Rheumatic Diseases. Prepared by THE COMMITTEE ON PUBLICATIONS OF THE AMERICAN RHEUMATISM ASSOCIATION, CHARLES H. SLOCUMB, M.D., Chairman; HOWARD F. POLLEY, M.D., WILLIAM D. ROBINSON, M.D., RICHARD T. SMITH, M.D., CHARLES RAGAN, M.D., EDWARD F. ROSENBERG, M.D., and CARLOS SACASA, M.D. 449 pages; 25.5 × 16.5 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $12.00.

Teratomas (Atlas of Tumor Pathology, Section III, Fascicle 9). By RUPERT A. WILLIS, D.Sc., M.D., F.R.C.P., Professor of Pathology, University of Leeds Medical School, Leeds, England. 58 pages; 26 × 20 cm. (paper-bound). 1951. Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. Price, 50 cents.

A Textbook of Clinical Neurology, with an Introduction to the History of Neurology. 7th Ed. By ISRAEL S. WECHSLER, M.D., Clinical Professor of Neurology, Columbia University, New York, etc. 801 pages; 24.5 × 16 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $9.50.

The Thoracic Surgical Patient—Preoperative, Anesthetic and Postoperative Care. By LEW A. HOCHBERG, M.D.; Foreword by FRANK B. BERRY, M.D. 364 pages; 23.5 × 15.5 cm. 1952. Grune & Stratton, New York. Price, $8.75.

Die Transfusion von Konserviertem Blut in der Geburtshilfe und Gynäkologie. By PROF. DR. H. SCHWALM. 132 pages; 24 × 17 cm. (paper-bound). 1952. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, Inc., New York. Price, Karton. DM 14.70.

Tumors of the Adrenal (*Atlas of Tumor Pathology, Section VIII, Fascicle 29*). By HOWARD T. KARSNER, M.D., Medical Research Advisor, Bureau of Medicine and Surgery, U. S. Navy, etc. 60 pages; 26 × 20 cm. (paper-bound). 1950. Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. Price, $1.00.

Tumors of the Breast (*Atlas of Tumor Pathology, Section IX, Fascicle 34*). By FRED W. STEWART, M.D., Pathologist to Memorial Hospital, etc. 114 pages; 26 × 20 cm. (paper-bound). 1950. Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. Price, $1.10.

Tumors of the Carotid Body and Related Structures (*Chemoreceptor System*) (*Atlas of Tumor Pathology, Section IV, Fascicle 16*). By PHILIP M. LECOMPTE, M.D., Pathologist, Faulkner Hospital, Boston, Massachusetts, etc. 40 pages; 26 × 20 cm. 1951. Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. Price, 45 cents.

Tumors of the Mediastinum (*Atlas of Tumor Pathology, Section V, Fascicle 18*). By HANS GEORGE SCHLUMBERGER, M.D., Professor of Pathology, Ohio State University, College of Medicine, Columbus, Ohio. 88 pages; 26 × 20 cm. (paper-bound). 1951. Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. Price, 75 cents.

Tumors of the Peripheral Nervous System (*Atlas of Tumor Pathology, Section II, Fascicle 6*). By ARTHUR PURDY STOUT, M.D., Professor of Surgery, Columbia University, College of Physicians and Surgeons, New York City. 57 pages; 26 × 20 cm. (paper-bound). 1949. Prepared at the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. Price, 60 cents.

COLLEGE NEWS NOTES

New Life Members

The College is gratified to announce that the following Fellows have become Life Members of the American College of Physicians since the publication of the last issue of this journal:

Dr. Kenneth D. A. Allen, Denver, Colo.
Dr. L. Dale Huffman, Los Angeles, Calif.
Dr. Edmund Jacobson, Chicago, Ill.
Dr. Friedrich W. Niehaus, Omaha, Nebr.
Dr. William Anton Henry Rettberg, Denver, Colo.
Dr. Milton E. Rose, Decatur, Ill.
Dr. Joseph D. McCarthy, Omaha, Nebr.
Dr. Edward R. Mugrage, Denver, Colo.
Dr. Samuel A. Weisman, Los Angeles, Calif.
Dr. William White Falkener, Hampton, Va.
Dr. Julius Ralph Pearson, Miami Beach, Fla.
Dr. John B. Hibbs, Uniontown, Pa.
Dr. Oscar Feinsilver, Worcester, Mass.
Dr. Joseph P. Brennan, Pendleton, Ore.
Dr. L. Mary Moench, New York, N. Y.
Dr. Michael Bevilacqua, Jamaica, N. Y.

A.C.P. Postgraduate Courses

Course No. 6, ELECTROCARDIOGRAPHY: Massachusetts General Hospital, Boston, Mass., Conger Williams, M.D., Director; May 12–17, 1952.

This course has been filled to capacity for several weeks and many applicants could not be accommodated this year. It is anticipated that greater facilities will be provided by the College for courses in this subject in the autumn.

Course No. 7, TRENDS AND NEWER DEVELOPMENTS IN INTERNAL MEDICINE: Hahnemann Medical College and Hospital of Philadelphia, Philadelphia, Pa., Charles L. Brown, M.D., F.A.C.P., Director; May 12–17, 1952.

Accommodations are still available in this course.

Course No. 8, PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE: University of Toronto Faculty of Medicine, Toronto, Ont., Can., Ray F. Farquharson, M.D., F.A.C.P., Director; June 2–6, 1952.

Places are available in this course but hotel accommodations have been largely exhausted. The Director, however, has arranged to accommodate registrants at the Men's and Women's University Residences (Dormitories). Adequate accommodations are still available.

The Committee on Postgraduate Courses met at Cleveland, April 21, 1952, and determined upon the schedule of courses for the autumn but this was too late for publication in this issue of the ANNALS. Therefore, a complete announcement will appear in the May issue.

Directory of the American College of Physicians

The 1951 Directory of the College was published as of October 1, 1951, although it did not come from press until the first of January, 1952. Some 3,000 members of the College and institutions subscribed in advance of publication and their copies have long since been delivered to them. However, a limited number of copies are still available to members; price, postpaid, $5.00.

A supplement to the 1951 Directory will be published during the summer of 1952, and will include corrections and additions to the last Directory.

Correction to 1951 Directory

The first line of the sixth entry on page 472 of the 1951 Directory of the College should be as follows (correction in first and middle names):

JONES, CHESTER MORSE (Internal Medicine, Gastro-enterology), A.B., M.D.

The Mid-South Regional Meeting

The Mid-South Regional Meeting covered the States of Arkansas, Louisiana, Mississippi, Oklahoma, Tennessee and Texas and was held at New Orleans, February 15–16, 1952, under the General Chairmanship of Dr. Thomas Findley, F.A.C.P. The States of Arkansas and Oklahoma held a combined Regional Meeting at Hot Springs, Ark., only a few months earlier, and Mississippi had also held its own individual Regional Meeting comparatively recently; these States, however, joined with Louisiana, Tennessee and Texas in the February meeting.

In view of the fact that members would have to travel long distances, it was determined to make this a two-day session rather than the usual one-day meeting, thus to make the trip more worthwhile. The two morning programs were devoted to clinical presentations at the Charity Hospital, there being programs presented by members of the Department of Medicine of the Ochsner Clinic, by members of the Department of Medicine of Louisiana State University School of Medicine, by members of the Medical Section of the Veterans Administration Hospital, and by members of the Department of Medicine of Tulane University of Louisiana School of Medicine. The afternoon sessions were held at the Roosevelt Hotel, and the programs consisted of formal presentations by members or guests from the participating States. One feature was a clinicopathological conference at which Dr. Maurice C. Pincoffs, President of the College, was the diagnostician and Dr. Charles E. Dunlap, Professor of Pathology at Tulane University, the pathologist.

A reception, cocktail party and banquet were held at the Roosevelt Hotel on the evening of February 15, with President Pincoffs, Executive Secretary Edward R. Loveland, and the Honorable Jimmy Arrington, Mayor of Collins, Miss., speakers. A program of entertainment was arranged for the visiting ladies, of whom there were over fifty registered.

Attendance at this meeting was particularly gratifying, attesting to the excellence of the program:

Arkansas	12	(27% member attendance)
Louisiana	72	(48% member attendance)
Mississippi	23	(62% member attendance)
Oklahoma	18	(23% member attendance)
Tennessee	27	(25% member attendance)
Texas	90	(20% member attendance)

Attendants came from fifteen additional states, and there was one guest from England. The summary of the attendance, exclusive of the ladies, was: 1 Master; 125 Fellows; 71 Associates; 97 guests; Total, 294.

Puerto Rico Regional Meeting Held at San Juan

The Annual Regional Meeting of the American College of Physicians for Puerto Rico was held at San Juan, February 17, 1952, under the Governorship of Dr. R. Rodriguez-Molina, F.A.C.P. An excellent program, to which Fellows and Associates of the College and some invited guests contributed, was presented. Members of the Puerto Rico Medical Association were invited and many were in attendance. Dr. T. Grier Miller, Philadelphia, President-Elect of the College, represented the College and addressed the Banquet on "The Functions of the American College of Physicians."

Delaware, District of Columbia and Maryland Regional Meeting

The Annual Regional Meeting for the District of Columbia and Maryland, in which Delaware also joined, was held at Johns Hopkins Hospital, Baltimore, March 1, 1952, with a total attendance of 1 Master, 60 Fellows, 19 Associates and 46 guests —126. Although the attendance was quite satisfactory, it would have been very much greater had not a sudden snow storm badly affected travel, reducing the attendance from outlying districts. As usual, the program was a very excellent one, and instead of holding the usual banquet and reception in the evening, a special luncheon was given in the Doctors' Dining Room of the Hospital, and the gathering was addressed by Dr. M. C. Pincoffs, President of the College, and by Mr. E. R. Loveland, Executive Secretary. It is planned to hold the next Regional Meeting for that district earlier in the year and at Washington in 1953.

Nebraska Regional Meeting

The Annual Regional Meeting for the State of Nebraska was held at Lincoln, Nebraska, February 23, 1952, under the Governorship of Dr. Joseph D. McCarthy, F.A.C.P., and the General Chairmanship of Dr. Floyd L. Rogers, F.A.C.P., of Lincoln. There was an excellent program, highlighted by several excellent papers including a presentation by Dr. LeRoy H. Sloan, F.A.C.P., of Chicago, who was the official representative of the Board of Regents of the College. Though restricted due to a snow and sleet storm, the attendance was quite satisfactory, including 49 members and 19 guests, a total of 68. The banquet in the evening was addressed by Dr. Sloan, as the Vice-President of the College, and by Dr. Joseph D. McCarthy, Governor for Nebraska. The 1953 Regional Meeting will be held during the month of February in Omaha.

Colorado Regional Meeting

A Regional Meeting of the American College of Physicians for the states of Idaho, New Mexico, Montana, Wyoming and Colorado was held at Denver, February 12, 1952, under the General Chairmanship of Dr. Ward Darley, F.A.C.P., Governor for Colorado, and with the active coöperation of the College Governors for Idaho, New Mexico, Montana and Wyoming, Drs. Richard P. Howard, F.A.C.P., Walter I. Werner, F.A.C.P., and Harold W. Gregg, F.A.C.P., respectively. Dr. Abe Ravin,

F.A.C.P., was chairman of the program committee, and arranged an exceedingly fine program.

The Colorado Society of Internal Medicine, the Medical Society of the City and County of Denver and the Colorado State Medical Society Midwinter Clinics arranged some of their functions immediately preceding the Regional Meeting and participated in the College program and banquet. Dr. Dwight L. Wilbur, F.A.C.P., San Francisco, Regent of the College, was its official representative and addressed the meeting on "The Clinical Aspects of Portal Hypertension." Dr. Wilbur was also the guest speaker at the banquet, his subject being "Management of the Nervous and Exhausted Patient." The banquet was followed by a smoker for registrants for the Midwinter Clinics. By having all these meetings in approximation, the benefit of each meeting was available to all and the place of the American College of Physicians was more forcibly emphasized.

The program was probably the best in the history of the Colorado Regional Meeting and was received with much enthusiasm. There were in attendance 57 members of the College and 51 guests, or a total of 108.

Virginia Regional Meeting

The Annual Regional Meeting of the Fellows and Associates of the American College of Physicians for Virginia was held at Charlottesville, February 28, 1952, under the Governorship of Charles M. Caravati, M.D., and the Chairmanship of Dr. Byrd S. Leavell, F.A.C.P. Dr. Thomas S. Edwards (Associate), Dr. James B. Twyman (Associate), and Dr. John L. Guerrant, F.A.C.P., all of Charlottesville, were responsible for entertainment, arrangements and program, respectively. Dr. James F. Waddill, F.A.C.P., of Norfolk, is the Secretary of the Virginia section.

The program was devoted very largely to investigative, new work, and proved thoroughly interesting. There were registered a total of about 150 doctors coming from all parts of Virginia. A social hour and banquet were held at the Monticello Hotel in the evening. The Toastmastership was shared by Dr. Byrd S. Leavell and by Dr. Charles M. Caravati. An address concerning College activities was made by Mr. E. R. Loveland, the Executive Secretary of the College. Dr. Walter B. Martin, Vice President of the College, gave a most thoughtful and searching talk concerning the matter of requirements for membership and the recent discussions concerned with radical changes in the College structure. The subject was open for general discussion among the members, and revealed a very active and keen interest on the part of the members in any proposal that affects the general character of the organization. Among special guests were Dr. Paul H. Revercomb, F.A.C.P., College Governor for West Virginia, and Dr. Elbert L. Persons, F.A.C.P., College Governor for North Carolina.

Gift to the College Library of Publications by Members

Dr. David J. Sandweiss, F.A.C.P., Detroit, Mich., has presented the College Library of Publications by Members with an autographed copy of his book, "Postgraduate Medicine and Surgery: Peptic Ulcer," which he edited under the auspices of the American Gastroenterological Association.

The College Library of Publications by Members is maintained at College Headquarters. Members frequently present copies of their books to the College and thus the Library has become a living memorial to the member-authors.

The First International Congress of Dietetics will be held July 7–11, 1952, in the Royal Tropical Institute, Amsterdam, Netherlands. Persons who are interested are kindly requested to apply for further details to: Miss Diane J. Ten Haaf, General Secretary, Executive Committee, 13 Pomonaplein, The Hague, Netherlands.

The Thirteenth Annual Meeting of the Society for Investigative Dermatology, Inc., will be held at Chicago, Ill., June 7–8, 1952. Among the speakers on the program are Dr. John R. Haserick (Associate), Cleveland, Ohio, "Studies on the L. E. Factor"; Dr. Walter B. Shelley, F.A.C.P., Ardmore, Pa., and Dr. Harry J. Hurley, Jr., "The Physiology of the Human Apocrine Sweat Gland"; and Dr. Arthur C. Curtis, F.A.C.P., Charlottesville, Va., Dr. Clayton E. Wheeler and Dr. Edward P. Cawley, "The Effects of Topically Applied Hormones on Nipple Growth and Pigmentation."

Postgraduate Refresher Courses Arranged by Eighth United States Army, Korea

Through the coöperation of the Surgeon, EUSAK, and the Commanding Officers of the Military Hospitals in Korea, postgraduate refresher courses in Medicine and Surgery, and their subspecialties, are being organized. The first such course was organized in the field of Diseases of the Chest which consisted of a concentrated three-day series of lectures, demonstrations, motion pictures, case presentations and discussion periods. Dr. Donald S. King, F.A.C.P., of Boston, Mass., was a guest member of the faculty, and Col. Walter M. Bartlett, F.A.C.P., Medical Consultant, EUSAK, served as Chairman of two of the evening sessions, which were combined meetings with the members of the Pusan UN Medical and Dental Society. The course was given February 20, 21 and 22, 1952, and other courses are planned for the future.

Postgraduate Courses Offered in Brooklyn

The State University of New York College of Medicine and the Medical Society of the County of Kings is offering a number of postgraduate courses during the spring of 1952, including: Electrocardiography for the General Practitioner; Advanced Cardiology and Electrocardiography; Cardiovascular Disease—Clinical and Electrocardiographic Correlation; Clinical Cardiology; Clinical Ballistocardiography; Clinical Neurology; Clinical Hematology; Gastroenterology; Gastroscopy; Arthritis; Diseases of the Chest; Internal Medicine; Metabolic Endocrinology; Treatment of Peripheral Vascular Diseases; Clinical Radiology; Roentgen Diagnosis in Gastroenterology; Cardiovascular Roentgenology; Dermatology for the General Practitioner, and several others. These courses, however, are organized for the most part for local physicians, and meet one or two sessions per week over a series of several weeks. Application for admission should be made to the Joint Committee on Postgraduate Education at the Medical Society Building, 1313 Bedford Avenue, Brooklyn 16, N. Y.

The Second Annual Institute in Psychiatry and Neurology was held April 16, 1952, at the Veterans Administration Hospital, Lyons, N. J. Among the guest lecturers were Dr. Harvey J. Tomkins, F.A.C.P., Chief of the Psychiatry and Neurology Division, Veterans Administration, Washington, D. C.; Dr. Daniel Blain, F.A.C.P., Medical Director, American Psychiatric Association, Washington, D. C.; and Dr.

Edward G. Billings, F.A.C.P., Clinical Associate Professor of Psychiatry, University of Colorado School of Medicine, Denver, Colo. There were six clinical demonstrations and ten medical exhibits by the hospital staff. Dr. Crawford N. Banganz, F.A.C.P., is the Manager of the Lyons Veterans Administration Hospital.

The Texas Academy of Internal Medicine met January 19–20, in Galveston. Dr. W. Clay Dine, F.A.C.P., Amarillo, was elected President and Dr. Alfred W. Harris, F.A.C.P., Dallas, was elected Vice President. Among those elected to the Board of Governors were Dr. Robert A. Hettig (Associate), Houston, and Dr. Percy K. Smith, F.A.C.P., Wichita Falls.

Among the speakers on the program were Dr. George R. Herrmann, F.A.C.P., Galveston, "Investigations of Sodium Metabolism of Heart Disease under Treatment"; Dr. Ramond L. Gregory, F.A.C.P., Galveston, "Further Studies Concerning the Pathogenesis of Hypertension"; Dr. John W. Middleton (Associate), Galveston, "Tuberculous Meningitis"; and Dr. William C. Levin, F.A.C.P., Galveston, "Clinical Interpretation of Bone Marrow Biopsy." Dr. Edward J. Lefeber, F.A.C.P., Galveston, joined with Charles M. Pomerat, Ph.D., in presenting "Tissue Cultures of Pleural Fluids."

The Philadelphia County Medical Society conducted its 16th Annual Postgraduate Institute and Convention, April 1–4, 1952. A very complete program was presented, including panel discussions, symposia and colored televised clinics.

One of the panels, "Functional Problems in General Practice," was under the chairmanship of Dr. Edward Weiss, F.A.C.P. On this panel, Dr. O. Spurgeon English, F.A.C.P., discussed "Psychotherapy in General Practice." Dr. George Morris Piersol, M.A.C.P., was Chairman of a Television Clinic presented from the Curtis Clinic of the Jefferson Medical College Hospital under the topic, "Application of Physical Medicine to the Management of Various Physical Handicaps." As part of the symposium, "Pediatric Problems," Dr. Carl C. Fischer, F.A.C.P., spoke on "The Management of Convulsions in Infancy and Childhood." Dr. John Lansbury, F.A.C.P., was Chairman of the panel, "ACTH, Cortisone and Hydrocortisone." Dr. Joseph L. Hollander, F.A.C.P., covered the "Rheumatologic Aspects" on this panel. Dr. Henry L. Bockus, F.A.C.P., and Dr. Truman G. Schnabel, F.A.C.P., served as Clinicians for the Clinical-Pathological Conference.

The sixth annual meeting of the National Society for Medical Research was held February 10, in Chicago, Ill. Dr. Anton J. Carlson, M.A.C.P., Chicago, Ill., President, reported a year of unprecedented progress. Numerous states have passed affirmative laws relating to animal experimentation. The basis for these laws is the desire to make available, for scientific use, those unclaimed, unwanted animals which would otherwise be destroyed in public pounds. Dr. Carlson also reported that seventeen organizations have been added to the roster of member associations, bringing the total to 274. The Society also has several new publications in the process of completion.

At the conclusion of the meeting, Dr. Carlson and Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., were re-elected President and Secretary-Treasurer, respectively.

Commission on Accreditation of Hospitals

Dr. Gunnar Gunderson of LaCrosse, Wis., has been appointed Chairman of the recently incorporated Commission on the Accreditation of Hospitals. This Commis-

sion, representing organized medicine and hospitals of two great nations—the United States and Canada—will be a great force in the world for improving institutional care of the sick and injured.

The members of the Commission from the American College of Physicians include Drs. LeRoy H. Sloan, F.A.C.P., Chicago, Ill.; Alex. M. Burgess, F.A.C.P., Providence, R. I.; and William S. Middleton, F.A.C.P., Madison, Wis.

A. M. A. Council on Medical Service

For several years the Council's Physicians Placement Service has assisted physicians seeking locations and has helped communities secure the services of physicians. During the past year interest in physician placement and distribution of physicians has increased greatly, and a majority of the state medical associations are now conducting placement bureaus.

While the Council on Medical Service and the state bureaus are designed primarily to interest physicians in general practice in communities without physicians, many requests are received from specialists. Because of this the Council's Committee on Extension of Hospitals and Other Facilities has suggested that the Council coördinate its program with any similar programs that might be carried on by specialty societies. The American College of Physicians does not handle placement of physicians and thus recommends that any physician interested in placement or any community interested in obtaining a physician or specialist, shall communicate with the Council on Medical Service of the American Medical Association, 535 N. Dearborn St., Chicago, 10, Ill.

Diabetes–The Journal of the American Diabetes Association

The American Diabetes Association has just inaugurated a new bimonthly scientific publication, *Diabetes*, which will be the official journal of the Association with the purpose of disseminating important data about the nature, diagnosis, and treatment of diabetes and its complications. The Editor of the new journal is Dr. Frank N. Allan, F.A.C.P., Executive Director of the Medical Department of the Lahey Clinic in Boston, Mass. Of a total of 17 members of the Editorial Board, 11 are Fellows of the American College of Physicians: Dr. Edward L. Bortz, Philadelphia, Pa.; Dr. Arthur R. Colwell, Chicago, Ill.; Dr. Jerome W. Conn, Chicago, Ill.; Dr. Blair Holcomb, Portland, Ore.; Dr. E. Perry McCullagh, Cleveland, Ohio; Dr. Alexander Marble, Boston, Mass.; Dr. Franklin B. Peck, Indianapolis, Ind.; Dr. Henry T. Ricketts, Chicago, Ill.; Dr. Randall G. Sprague, Rochester, Minn.; Dr. Russell M. Wilder, Bethesda, Md.; and Dr. Wallace M. Yater, Washington, D. C.

American Library Service

The American Library Service, 117 W. 48th St., New York 19, N. Y., announces that it has in its file an outstanding collection of reprints of important articles that have appeared in medical journals (many of them with limited circulation) during the past sixty years. Much of this material is no longer available through the usual channels of purchasing. Much of this material would prove to be of the utmost interest to the individual specialists, or to the hospital or university library, as well as to the research student and historian.

The American Library Service has determined to make these publications avail-

able for purchase by libraries or individuals at a nominal cost. It will be happy to furnish upon request at no obligation a list of available items on any specified subject.

Dr. Paul B. Beeson, F.A.C.P., has resigned as Professor of Medicine and Associate Professor of Bacteriology, Emory University School of Medicine, Atlanta, to accept an appointment as Ensign Professor of Medicine and Chairman of the Department of Internal Medicine, Yale University School of Medicine, succeeding the late Dr. Francis G. Blake.

Dr. Francis J. Braceland, F.A.C.P., Psychiatrist-in-Chief of the Institute of Living, Hartford, Conn., was elected President of the American Board of Psychiatry and Neurology at its Annual Meeting in December, 1951. At the same time Dr. Bernard J. Alpers, F.A.C.P., Professor of Neurology at Jefferson Medical College of Philadelphia, was elected Vice President. The Board will hold its next meeting in Chicago in June, 1952, at which time examinations of candidates will be conducted at the Neuropsychiatric Institute of the University of Illinois.

Dr. Samuel G. Feuer (Associate), Brooklyn, N. Y., was recently appointed Associate Attending in the Department of Medicine at St. John's Episcopal Hospital, in charge of a new Department of Physical Medicine and Rehabilitation.

Dr. John C. Ruddock, F.A.C.P., Medical Director of the Richfield Oil Corporation, Los Angeles, was recently elected an Honorary Member of the Royal Society of Medicine of London, England, "in recognition of distinguished services to science."

Among the guest speakers at the Annual Congress of the American College of Allergists, which was held in Pittsburgh, April 7–9, were Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill., "Allergy to Drugs"; and Dr. Leo H. Criep, F.A.C.P., Pittsburgh, Pa., "Regional Factors in Allergic Disease."

Dr. Irving S. Wright, F.A.C.P., College Governor for Eastern New York, was the official representative of the American College of Physicians at the dinner meeting of the Board of Directors of the United States Committee of the World Medical Association at New York on March 11, 1952.

Edward Harvey Cushing, M.D., F.A.C.P., has announced his resignation as Assistant Chief Medical Director of the Veterans Administration and head of its Research and Education Service as of March 1, 1952.

Dr. Garfield G. Duncan, F.A.C.P., Clinical Professor of Medicine, Jefferson Medical College of Philadelphia, delivered the fifth annual Stoneburner lecture series at the Medical College of Virginia, Richmond, March 19–20. Dr. Duncan's first lecture was "Management of Diabetes Mellitus" and his second was "Consideration of the Undernourished Patient."

Dr. Jacob C. Geiger, F.A.C.P., resigned March 1, as Director of Public Health of the City of San Francisco. Dr. Geiger will undertake similar work in the Department of Public Health in the City of Oakland. He served San Francisco for 20 years and the San Francisco Medical Society credits him with having developed one of the most efficient emergency systems in the United States.

Dr. Henry J. Bakst, F.A.C.P., Boston, Mass., was recently named Professor of Preventive Medicine and Head of the Genital Infection Department of Boston University and of the Massachusetts Memorial Hospitals.

Dr. W. Barry Wood, Jr., F.A.C.P., Busch Professor of Medicine at Washington School of Medicine, St. Louis, served as Physician-in-Chief pro tempore at the Peter Bent Brigham Hospital in Boston during the week of January 14, 1952.

OBITUARIES

DR. FRANCIS GILMAN BLAKE

Francis Gilman Blake, A.B., M.D., F.A.C.P., died at Walter Reed Army Hospital in Washington, D. C., of coronary thrombosis on February 1, 1952. He had had a previous attack in September, 1951. He had been on duty as Civilian Consultant to the U. S. Army for only twelve days when taken ill.

Actual retirement as Sterling Professor of Medicine at Yale University School of Medicine took place in 1951. Formally he was to retire in June, 1952. He was born in 1887 in Mansfield Valley, Pa. His premedical work was done at Dartmouth College where he received his A.B. degree in 1908. His medical work was done at Harvard Medical School with graduation in 1913.

From 1913 to 1916 he was at Peter Bent Brigham Hospital as Interne, Assistant Resident and Resident. From 1916 to 1917, Moseley Travelling Fellow (Harvard), and Assistant in Medicine, Rockefeller Institute. Assistant Professor of Medicine, University of Minnesota and Attending Physician, Elliot Memorial Hospital, Minneapolis, 1917–1919; from 1919 to 1920, Associate in Medicine, Rockefeller Institute, New York; from 1921 to 1927, John Slade Ely Professor of Medicine and Physician-in-Chief to the New Haven Hospital (Yale); from 1927 to 1952, Sterling Professor of Medicine; Dean of Yale University School of Medicine from 1940 to 1947; a member of the Life Insurance Medical Research Fund; Diplomate of the American Board of Internal Medicine.

He was on active duty in the Army during World War I and was Chief of the Typhus Commission during World War II and President of the Armed Forces Epidemiological Board. For many years he had been a member of the National Advisory Health Council, United States Public Health Service, also Consultant to the Secretary of War.

Dr. Blake became a Fellow of the College in 1930; Governor for Connecticut, 1937–1939; Board of Regents, 1939–1947; Second Vice President, 1947–1948.

He made many contributions to American medicine, including his studies of pneumonia during World War I and later his studies with scarlet fever serum and its practical application. He was a leading American medical educator.

Dr. Blake was a retiring, quiet gentleman—not known well by a great many people—but dearly beloved and respected by those who did know him. His loss is widely felt.

THOMAS P. MURDOCK, M.D., F.A.C.P.,
Governor for Connecticut

DR. BYRON JAMES HUGHES

Byron James Hughes, B.S., M.D., Superintendent of the Winnebago State Hospital, Winnebago, Wis., died on January 15, 1952, in his forty-eighth year, from a cerebral hemorrhage, at Mercy Hospital, Oshkosh, Wis.

Dr. Hughes was born in Wyocena, Wis., on April 28, 1904. In 1929 he received his Bachelor of Science degree from the University of Wisconsin, and in 1931 he was graduated from the University of Wisconsin Medical School. Following an internship at Milwaukee County Hospital in 1931–1932, he entered state service to devote the rest of his life as a psychiatrist and administrator at the Winnebago State Hospital, first as a Resident Physician, then as an Institutional Physician, Assistant Superintendent, and Clinical Director. In 1939 he became Superintendent.

He was President of the Winnebago County Medical Society in 1946, Vice President of the Milwaukee County Neuropsychiatric Society from 1947 to 1948, Vice Speaker of the House of Delegates of the State Medical Society in 1950, and Speaker in 1951. For the State Medical Society he was also Chairman of the Medical Advisory Council on Veterans Affairs, and a member of the Committees on Mental Hygiene, Institutional Care, Public Welfare, and State Departments. He was Consultant at the Alexian Brothers Hospital at Oshkosh, and a member of the staff of Mercy Hospital, where he served on the Executive Council for the School of Nursing.

Much of the improvement in the care of the mentally ill in the state is accredited to Dr. Hughes. As an able hospital administrator, he took an active part in the planning and construction of the new Kempster Hall, completed as a 240-bed addition to Winnebago State Hospital, and used as a center of acute treatment of the mentally ill. As a consultant, he was collaborating in the development of a more realistic program for the rehabilitation of the chronically ill with interest especially in the chronic alcoholic.

Dr. Hughes was a Diplomate of the American Board of Psychiatry and Neurology, and was elected an Associate of the American College of Physicians in 1949.

KARVER L. PUESTOW, M.D., F.A.C.P.,
Governor for Wisconsin

MAJOR GENERAL EDGAR ERSKINE HUME

Major General Edgar E. Hume, the Army's most decorated medical officer, died on January 24, 1952, of a dissecting aneurysm of the abdominal aorta.

Born in Frankfort, Ky., December 26, 1889, General Hume received his M.D. degree from Johns Hopkins University School of Medicine, Baltimore, Md., in 1913. He continued his studies in Europe for several years and upon his return to the United States in 1916 was appointed First Lieutenant in the Medical Reserve Corps. He was sent to the Army Medical School, Washington, D. C., as a student and graduated from there in 1917, first in his class. He joined the Regular Army in January of that year.

One of his first Army assignments was with the Division of Sanitation, Office of the Surgeon General under General Gorgas in 1917. General Hume was the last member of General Gorgas' staff on active service.

He was assistant Librarian of the Army Medical Library, Washington, D. C., and worked as Editor of its Index Catalogue until April 1926, when he was named Medical Inspector and Epidemiologist at Fort Benning, Ga. He returned to the Library several years later as Librarian and served there until 1936.

Assigned to General Eisenhower's staff in North Africa in April, 1943, General Hume assisted in the planning for the invasions of Sicily and Italy, and participated in the initial landing at Salerno. He was in charge of the Allied Military Government in all the large cities of Italy and is the only U. S. officer who served in Italy in both World Wars.

In 1949, General Hume was named Chief Surgeon of the Far East Command on General MacArthur's staff and a year later General MacArthur appointed him Surgeon of the United Nations Command in Korea. In addition, he became Surgeon on the staff of the Supreme Commander for Allied Powers on June 15, 1951.

Since 1925, General Hume has been the United States Correspondent for the International Congresses of Military Medicine and a delegate to many of their meetings.

Among his many decorations are the Distinguished Service Medal with two Oak Leaf clusters, Silver Star with four Oak Leaf clusters, Purple Heart with four Oak Leaf clusters, Legion of Merit, Soldier's Medal, Bronze Star with three Oak Leaf clusters, Navy Bronze Star, Typhus Commission Medal, Commendation Ribbon with three Oak Leaf clusters, Air Medal with two Oak Leaf clusters and 37 foreign decorations.

General Hume, a member of Phi Beta Kappa, received numerous honorary degrees from American and foreign universities. He authored some 400 books and papers on scientific and historical topics. Fellow of the American Academy of Arts and Sciences, the American College of Surgeons and the American College of Physicians (1926), General Hume was also certified in Internal Medicine, in Neurology and in Preventive Medicine and Public Health.

GEORGE E. ARMSTRONG,
Major General, The Surgeon General,
A.C.P. Governor for the U. S. Army

DR. MARK PERRY SCHULTZ

Mark Perry Schultz, A.B., A.M., M.D., F.A.C.P., who retired on May 1, 1951, from the U. S. Public Health Service, where he played a prominent rôle in the field of cortisone research, died on May 26, 1951.

Born in Oxford, Ohio, November 4, 1899, Dr. Schultz received his A.B. degree from Miami University, Oxford, Ohio, in 1922, and his M.D. from Western Reserve University School of Medicine in 1926. His A.M. degree for work in internal medicine was also earned at Western Reserve University School of Medicine.

Dr. Schultz served his internship at Lakeside Hospital, Cleveland, Ohio, and from 1929 to 1932 was Assistant Resident Physician at the Hospital of the Rockefeller Institute. During the following year he served as Assistant at the Pathological Institute of the University of Leipzig, returning in 1933 to the Hospital of the Rockefeller Institute, where he spent the next two years as Assistant in Medicine.

In 1935, Dr. Schultz became Principal Specialist in heart disease investigation for the National Institutes of Health, principal research arm of the Public Health Service. A pioneer in cortisone research, he was among the first to realize its value in the treatment of acute rheumatic fever.

Commenting on Dr. Schultz' achievements, Dr. W. H. Sebrell, Jr., Director of the National Institutes of Health, stated: "In recent years, Dr. Schultz made notable contributions to our knowledge of the pathogenesis of rheumatic heart diseases. His work attracted to him research fellows from this country and abroad and his advice was frequently sought by professional colleagues in particularly difficult cases."

At the time of his retirement, Dr. Schultz was assigned to the Microbiological Institute of the National Institutes of Health, where he held the rank of Medical Director in the Laboratory of Infectious Diseases. In recent years he also served as Associate Visiting Physician at Children's Hospital, Washington, D. C. He

was the author of numerous articles dealing with rheumatic fever. Dr. Schultz was elected a Fellow of the American College of Physicians in 1938.

Prepared by the Office of the Surgeon General,
U. S. Public Health Service

DR. HARRY J. WHITE

Harry J. White, M.D., Troy, N. Y., was born in Troy, N. Y., on July 13, 1878, and died on December 11, 1951, from general carcinomatosis of the abdomen. He graduated from the Albany Medical College in 1899, served as Interne at the Albany Hospital and later as Resident at the Samaritan Hospital in Troy. He was later appointed Attending Physician at the Samaritan Hospital, became Chairman of the Medical Staff of that hospital in 1921 and subsequently served as Chief of the Medical Staff. He also was Attending Physician at the Leonard Hospital in Troy.

Dr. White was known as a family physician. His practice extended over a period of fifty years. He was very highly respected by his patients and colleagues. He became an Associate of the American College of Physicians in 1923 and attended many of its meetings.

He is survived by his wife, Mrs. Ruth Freeman White, two sons, Henry R. White and William B. White of Troy, and a daughter Mrs. Walter S. Hunt.

Edward C. Reifenstein, Sr., M.D., F.A.C.P.
Governor for Western New York

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